HEARING LOSS AND LATE-LIFE MENTAL HEATLH

by

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ABSTRACT

Background

Given the rapidly aging population, the global pace of research has accelerated with regards to potentially modifiable risk factors for dementia, including hearing loss. While there is a growing body of knowledge on the association between hearing loss and dementia, significant gaps remain.

Objectives

Our objective is to further characterize and provide context to our current knowledge of the association between hearing loss and dementia. We first complete an in-depth review of available evidence geared towards audiologists and auditory scientists, and provide clinical implications and ideas for future directions (Aim 1, Chapter 2). We then evaluate how hearing loss fits within the broader framework of risk for dementia and late-life mental health conditions, both as it may influence other risk factors (i.e., depression) (Aim 2, Chapter 3) as well as how the combination of both risk factors may further influence cognitive outcomes, including cognitive decline and dementia (Aim 3, Chapter 4).

Methods

For Aims 2 and 3, we leveraged data from the Health, Aging, and Body Composition Study, a longitudinal cohort of high-functioning community-dwelling older adults aged 70-79 years at baseline (1997-1998) from Memphis, Tennessee or Pittsburgh, Pennsylvania. In Aim 2, we compared varied definitions of depressive symptomatology to assess prevalence, incidence, and trajectory of change of symptomatology over time by category of hearing loss using logistic

regression, discrete-time proportional hazard models, and generalized mixture models followed by multinomial logistic regression, respectively. In Aim 3, we similarly use multiple means of operationalizing depressive symptomatology to investigate if the additional presence of depressive symptoms among those with hearing loss alters rates of cognitive decline or risk for incident dementia using linear mixed effects models and Cox proportional hazard models.

Results

Results of our primary analysis indicate that 1) hearing loss is associated with increased risk for depressive symptomatology in older adults; 2) a moderate or greater hearing loss alone leads to faster rates of cognitive decline and greater risk for incident dementia; and 3) individuals with hearing loss who additionally developed depressive symptoms overall presented the greatest estimated risk for both rates of cognitive decline and risk of incident dementia.

Conclusions

Hearing loss may increase risk for late-life mental health conditions including depressive symptomatology, cognitive decline, and dementia. Consideration of hearing loss and its management within the context of other dementia risk factors, may aid in intervention and prevention strategies for late-life cognition. Continued targeted investigation of the hearing-depression-dementia association has potential for far-reaching public health benefit for older adults, their loved ones, and our aging society.

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CHAPTER 1: Introduction

1.1 Overview

Given the rapidly aging population, the global pace of research has accelerated with respect to potentially modifiable risk factors for dementia, including hearing loss. While there is a growing body of knowledge on the association between hearing loss and dementia, significant gaps in our understanding remain[1]. The work presented here first aims to highlight these gaps within the context of what we currently know regarding hearing loss and dementia. We posit ways in which we might conduct targeted research to address such gaps. A comprehensive review of dementia, current evidence on the association between hearing loss and dementia, and proposed mechanism(s) behind the association is thoroughly discussed in Chapter 2. We consider how hearing loss may potentially fit into a broader framework of late-life mental health and risk factors for dementia. We quantify how hearing loss might increase risk for depressive symptoms- itself an independent risk factor for dementia[2], and which presents opportunity for intervention along the pathway to dementia. We lastly investigate how the additional presence of depressive symptoms among those with hearing loss might alter dementia risk for hearing impaired older adults.

Our overall objective is to further characterize and provide context to our current knowledge of the association between hearing loss and dementia. With the high prevalence of hearing loss, understanding how this impairment may influence other risk factors for dementia, or how the combined effect of additional factors among hearing impaired adults may influence risk for dementia may

present additional avenues for intervention strategies with widespread clinical and public health import.

1.2 Epidemiology of Dementia

In a 2020 report[1], the *Lancet* Commission on Dementia Prevention, Intervention and Care estimated up to 40% of dementia cases might be preventable through intervention on modifiable dementia risk factors. These risk factors include lower educational attainment, hypertension, smoking, obesity, depression, physical inactivity, diabetes, infrequent social contact, excessive alcohol consumption, head injury, air pollution, and notably, *hearing impairment*. Among these modifiable risk factors, it was estimated that intervention on hearing impairment could prevent or delay up to 8% of dementia cases. The disproportionate weight attributed to hearing loss is due, in part, to the high prevalence of hearing loss in the older adult population. It is estimated that two-thirds of adults over the age of 70 years have bilateral hearing loss, with significant growth in the population prevalence of hearing loss expected in the coming decades as the population ages[3-5]. In addition to its high prevalence, hearing loss has a strong relationship with dementia. Hearing impairment is associated with an estimated 94% increase in risk of dementia over time[6] compared to non-hearing impaired. We provide a more detailed discussion of dementia from a population-based perspective, review the current evidence for the hearing-dementia association, and discuss the potential mechanism(s) behind the relationship in Chapter 2 of this thesis. However, to understand where

auditory science and hearing health may fit into the broader picture of dementia prevention, we must first understand the role and presentation of dementia within the U.S. population.

1.2.1 The prevalence and cost of dementia care

In the U.S., an estimated 5.8 million individuals were living with Alzheimer's disease in 2020, with expected increase to nearly 14 million by 2050[5]. The growing prevalence of dementia translates to increased financial, social, and emotional burdens on both communities and families. The astronomical financial and emotional costs of dementia are among the many drivers behind the research for prevention or intervention at all stages of cognitive aging. Identification of additional avenues or means to enhance current strategies, particularly if intervention may influence multiple risk factors for dementia, has the potential to make substantial contributions to broader dementia prevention efforts.

1.2.2 Identifying Dementia

Cognitive decline may be thought of as a trajectory along a continuum spanning normal cognition, expected cognitive changes observed with aging, mild cognitive impairment (MCI), and dementia[7]. Cognitive decline then represents a change in cognitive functioning from an individual's prior ability[8]. While a general decrease in cognitive performance is anticipated with increasing age for many cognitive processes, particularly processing speed and memory[9], departures from prior ability greater than that expected for an individual's age and education suggests possible transition along the clinical spectrum.

Importantly, defined cut-points between age-expected cognitive ability, MCI, and dementia currently do not exist. Therefore, diagnoses are made based on clinical expertise and judgement and may be supported by pathophysiology (e.g., labs, imaging) if available[7].

Clinical diagnosis of dementia is made by a careful history and physical exam, cognitive testing, laboratory, and imaging studies[10]. Neurocognitive evaluations are instrumental components in a provider's clinical examination of a patient's cognitive status. The assessments evaluate global cognitive performance or cognitive ability within five recognized cognitive domains: memory, attention, executive function, language, and visuospatial. This variety of available cognitive tests are completed across visual and auditory modalities.

1.2.3 Dementia Prevention

What remains clear is that the expected growth in dementia cases worldwide requires action on dementia prevention and intervention, as currently there is no FDA approved disease modifying treatment for Alzheimer's disease and related dementias. Current treatment considerations for most forms of dementia have the goal of delaying or minimizing the impact of clinical symptoms for a period of time[1]. In the absence of a cure, the primary objective of epidemiologic research is to identify dementia risk factors associated with pathologic progression or dementia diagnosis, or identify factors associated with the progression of dementia symptoms. Subsequent goals of this research are to then identify opportunities to prevent or postpone dementia along the continuum. With identification of such risk factors, we may then emphasize research on the

implementation and delaying of dementia onset, which could have great implications at the population level. An intervention that could delay the onset of dementia by 5 years could lead to a 57% reduction in the number of patients with dementia[13] and 40% lower cost by 2050[11].

Research over the last few decades has sought to determine what role hearing loss may play in these global efforts for dementia prevention. Discussion of this research is completed in Chapter 2. With this thesis we aim to contribute to these efforts.

1.3 Hearing Loss in Older Adults

1.3.1 Epidemiology of Hearing Loss

The World Health Organization's 2021 *World Report on Hearing*[12] projected 1 in 4 people globally will have hearing difficulty by 2050 due to a global demographic shift to older populations. As previously stated, hearing loss has a high prevalence in older adults, doubling every 10 years after age 50[13] — its prevalence is 15% of those age 50-59 yet rises to 80% for those 85 and older in the United States. In addition to greater risk for diagnosis of hearing loss with increasing age, severity of hearing loss increases with each decade of life, with those over 80 years of age presenting a higher likelihood of moderate or greater hearing loss than mild hearing loss for the first time[4]. However, analysis in a nationally representative sample of older adults suggests the prevalence of hearing loss in the U.S. may be decreasing over the last decade[14], with an

estimated decrease of about 2% in adults compared to the prior decade. Improvements in health care or access to care and prevention of known risk factors for hearing loss likely contribute to this observed decrease.

Prevalence of hearing loss varies by non-modifiable factors such as certain identified syndromes and genetic factors[12]. Additional non-modifiable factors include race and gender with a lower prevalence of hearing loss noted among women compared to men and Black adults compared to Hispanic or non-Hispanic White adults[4, 13]. Characterizing differences in downstream effects of hearing loss by race and gender may offer opportunities for creative prevention strategies given differing social factors across subgroups which may influence neuropsychological outcomes[15-16].

Additional potential causative risk factors for hearing loss across the life course have also been identified[12]. While many risk factors for hearing loss stem from prenatal or perinatal causes/determinants (i.e., intrauterine infections, delivery complications), other risk factors for hearing loss in adolescence and adulthood have also been identified[12]. These include: otitis media (i.e., ear infections), viral infections or pathogens (i.e., measles, mumps, meningitis, HIV, Lassa virus, Ebola), chronic disease (i.e., hypertension, cardiovascular disease, diabetes), smoking, use of ototoxic medications, head trauma, excessive noise exposure from occupational, recreational, or environmental noise, ear-related conditions such as Meniere's disease, autoimmune disease, or vestibular schwannomas, and nutritional deficiencies from nutrients like Vitamin A, zinc, and iron. As stated, one of the greatest risk factors for hearing loss is increasing

age due to age-related sensorineural hearing loss. This is a multifactorial condition thought influenced by genetics, environmental factors, lifestyle, and illnesses. While it is not yet determined if all of these factors are causal, each is correlated with increased risk of hearing loss.

1.3.2 Measuring Hearing Ability

The act of hearing involves two inter-related processes and components of the auditory system – the peripheral hearing system and the central hearing system[17]- with unique measurement tools for each component. Both parts of the auditory system must work in tandem for an individual to appropriately detect and understand a sound. This process is essential for auditory interaction with the environment and for quality communication. Yet most commonly, it is the peripheral hearing system that is considered in discussion of hearing loss. The few epidemiologic studies that include a formalized measure of hearing primarily consider peripheral hearing ability alone. Moreover, many epidemiologic studies rely on self-reported measures of hearing. Self-report hearing considers perceived functional ability of hearing, incorporating aspects of the peripheral and central hearing system as well as the social environment and listening demands.

1.3.2.a Peripheral hearing system

The peripheral hearing system includes the outer ear (pinna), ear drum (tympanic membrane), middle ear bones (malleus, incus, and stapes) and cochlea[17] (**Figure 1.1a**). These components work together to channel the incoming auditory sound waves from the outer ear down the ear canal, and eventually encode the auditory information from the sound wave as an electrical

signal in the cochlea[17]. While a discussion of the complete anatomy and physiology of the peripheral hearing system is beyond the focus of this thesis, an individual's ability to detect the presence of auditory stimuli initiates within and is dependent upon the peripheral system.

The most common clinical tool for measurement of peripheral hearing acuity in adults is audiometry, with results graphically recorded on an audiogram[18]. The gold standard for testing is performed in a sound-proof booth using headphones. An auditory stimulus (i.e., pure tone) is presented at a particular frequency (Hz) at a given volume commonly within the range of 500-8000 Hz. The volume of each pure tone is lowered until the lowest volume level, the threshold in decibels hearing level (dB HL), at which the individual indicates detection of the tone. Results are often summarized as a four-frequency pure tone average (PTA), or the average of responses at 500, 1000, 2000, and 4000 Hz[18]. Consideration can be made if this average should be calculated from results from the better or poorer hearing ear depending on study question or objective.

1.3.2.b Central hearing system

Following passage through the peripheral auditory system, the electrical signal created by the cochlea is sent to the auditory nerve where it is then decoded by the brain[17] (**Figure 1.1b)**. Central hearing ability is therefore dependent upon the integrity of the auditory signal passed from the peripheral hearing system as well as additional cognitive processing[19]. While peripheral hearing ability may be simplified as the ability to detect sound, central hearing

ability then is the ability for the brain to understand and make sense of this sound, requiring significantly higher-level processing.

Measurement of central hearing is commonly completed through the presentation of speech within the presence of increasing volume of background noise (i.e., speech-in-noise testing) or specialized tests of central auditory processing ability[19], but is far less frequently completed in both clinical visits as well as in large scale epidemiologic studies. This interdependence between central hearing ability and cognitive processing blurs the distinction between the two processing abilities. In addition, heterogeneity in prior study of this work has created significant barriers to pooled evidence and causal inference regarding the role of central hearing ability in late-life mental health. While beyond the scope of this dissertation, a functional understanding of both aspects of the hearing system is important when considering dementia prevention strategies.

1.3.3 Modifiability of hearing loss

Historically, hearing loss has been considered a benign component of the aging process resulting primarily in impaired communication. However, research over the last few decades has highlighted hearing loss as a precipitating factor for additional functional and neuropsychiatric disorders in older adults and has spurred changes in thought within the medical and public health community[20-22]. Importantly, hearing loss is generally considered modifiable through amplification. Therefore, the scientific and clinical community has begun to recognize the potential protective benefit of hearing loss management, particularly for neuropsychiatric conditions such as depression and dementia[2].

Therapeutic opportunity exists, as hearing aids are vastly underutilized: on average only ~30% of eligible adults obtain hearing aids[13]. While significant barriers and disparities in hearing health care and accessibility of care and services remain, the potential room for intervention growth and public health benefit is substantial. Management of hearing loss through amplification options may not only decrease risk for neuropsychiatric conditions[2], but may also improve treatment adherence, patient satisfaction, and improve overall health-related quality of life for older adults[23]. Understanding subgroups who may receive particular benefit from increased amplification use may therefore save health care costs, reduce burden, and improve outcomes.

1.4 Hearing loss in the presence of other geriatric conditions

What has received considerably less study is how the presence of hearing loss, in combination with other complex geriatric conditions, which themselves may serve as risk factors for dementia may modify dementia risk and other psychosocial outcomes for older adults. Around 67% of older adults of Medicare age have multimorbidity[24]. Given the high prevalence of hearing loss, hearing impairment is likely present in older adults along with other health conditions. Therefore, the study of differences in dementia risk by subgroups of older adults with concurrent modifiable risk factors for cognitive decline could have meaningful public health benefit.

In the *Lancet* report[1], late-life depression was thought to contribute to nearly 4% of potentially preventable dementia cases. Similar to hearing loss, late-life depression presents a 90% greater risk of dementia; however, the lower prevalence of diagnosed depression at 13.2% contributes to the lesser-weighted fraction of potentially preventable cases[1]. Much remains to be clarified in how diagnosed depression or the presence of clinically significant depressive symptoms is associated with dementia, as depression is currently recognized as both a risk factor and a prodromal sign of dementia[1]. Importantly, while evidence is mixed, prior work suggests hearing loss may increase risk of depression or depressive symptoms in older adults[25-28]. However, prior research has not accounted for the heterogeneous course of depressive symptomatology over time. Older adults with hearing loss may avoid social situations or have difficulty engaging with surroundings and loved ones due to difficulty communicating in challenging listening situations. Further, changes in brain structure due to hearing loss may lead to elevated vulnerability for depressive symptomatology or result in behaviors that can increase social isolation and risk for depression[2]. Recent hypotheses suggest the psychosocial effect of hearing loss may differ not only by environment and listening needs, but also by race and gender. While it is unclear if depressive symptoms may mediate or modify the hearing and dementia association, it is valuable from clinical and public health lenses to quantify how the presence of these risk factors influence cognitive outcomes. Elucidation of the complex relationship between hearing loss, depressive

symptoms and dementia may present novel opportunity for public health prevention and intervention options for dementia in older adults.

1.5 Study Description

The work presented in this thesis addresses gaps in our understanding of the clinical relevance and public health burden of hearing loss on late-life mental health. Quantifying the role that hearing loss may have within the milieu of late-life mental health may present underutilized opportunities for intervention and prevention efforts, as depicted in our conceptual framework (**Figure 1.2**).

1.5.1 Health, Aging, and Body Composition Study

The analyses conducted and presented here in Chapters 3 and 4 use data from the Health, Aging, and Body Composition Study (Health ABC). The Health ABC study, began in 1997-1998, is a prospective study with up to 16 years of follow-up. The study was designed to evaluate risk factors associated with a decline in function in healthier older adults, including evaluation of differences in the onset of functional limitations, disability, and longevity by sex and race (Black vs White). Of particular benefit to our work was a focus when designing the study to allow for assessment of multi-morbidity on these outcomes. The study enrolled 3,075 well-functioning, community-dwelling Black or White older men and women aged 70-79 years at baseline from Pittsburgh, Pennsylvania and Memphis, Tennessee[29]. Participants were selected for inclusion in this study if they reported no difficulty walking ¼ mile or climbing up 10 steps. Follow-up consisted of yearly clinical examinations and 6-month interim phone calls, terminating in

2013. Audiometry was conducted at the study visit during the 5th year of follow-up.

1.5.2 Aim 1: Hearing and Cognition in an Aging World

In Chapter 2, we present a comprehensive review of the state of the research on the association between hearing loss and dementia. We (1) provide a foundational understanding of dementia epidemiology, presentation, and diagnosis in the United States; (2) contextualize research on the association between hearing loss and dementia to guide dementia prevention and intervention; (3) review mechanistic theories about the hearing-dementia association; (4) review priorities for future research; and (5) provide a perspective on how we can utilize current and future evidence to improve patient care. We conclude by presenting a call for multi-disciplinary collaboration for the advancement of our understanding of the hearing-dementia association and future intervention strategies.

1.5.3 Aim 2: Hearing Loss and Risk of Depressive Symptoms in Older Adults

The purpose of this study was to investigate if hearing loss is associated with greater prevalence of depressive symptoms, greater incidence of depressive symptoms, or is associated with a greater increase in depressive symptoms over time. We further investigate racial and gender differences in the association. We hypothesized hearing loss is associated with greater risk for the presence and new occurrence of depressive symptoms as well as larger changes in severity of depressive symptoms, particularly among women and Black participants. Our

study included varied measures of depressive symptoms to attempt to capture the heterogeneous course of depression in older adults. We used logistic regression to investigate the odds of clinically significant depressive symptoms by hearing status, and discrete-time proportional hazard models to quantify risk of incident clinically significant depressive symptomatology. Lastly, we used generalized mixture modeling to create classifications of trajectories for change in depressive symptoms over time. We then used multinomial logistic regression to describe the relative risk ratio of belonging to a particular depressive symptom trajectory by hearing status.

1.5.4 Aim 3: Examining the Combined Estimated Effects of Hearing Impairment and Depressive Symptoms on Risk of Cognitive Decline and Incident Dementia

In our last paper, we aimed to test if (i) rates of cognitive change and (ii) risk of incident dementia, differ for participants with both hearing loss and depressive symptoms compared to what would be expected given their independent effects. We hypothesized the additional presence of depressive symptomatology among hearing impaired older adults demonstrates faster rates of cognitive decline and greater risk of incident dementia. We created a four-category exposure for this analysis 1) normal hearing or mild loss (reference category), 2) moderate or greater hearing loss only, 3) clinically significant depressive symptoms only, and 4) both moderate or greater hearing loss and clinically significant depressive symptoms. We again used multiple measures of depressive symptomatology to try to incorporate the heterogeneous course of

symptomatology over time. We used linear mixed effects models with subject specific slopes and intercepts to evaluate rates of cognitive change over up to 8 years of follow-up by hearing and depression status. We then aimed to evaluate risk for incident dementia by hearing and depression status using Cox proportional hazard models with investigation on both the additive and multiplicative scale.

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approached in the Health ABC study. *J Gerontol A Biol Sci Med Sci*. 2001; 56(10): M644-M649.

FIGURE 1.3 The auditory system.

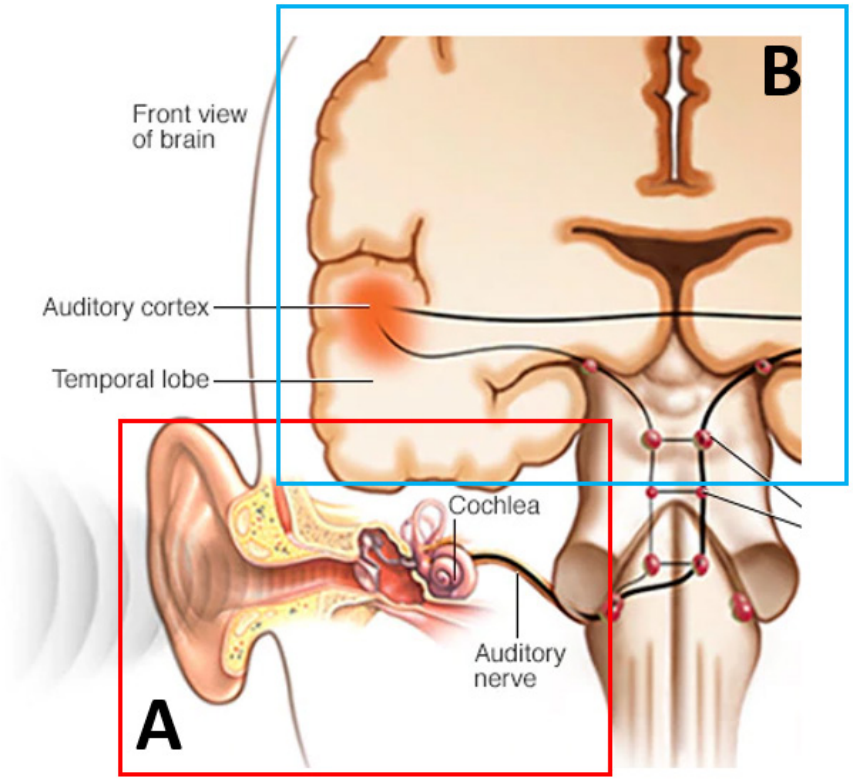
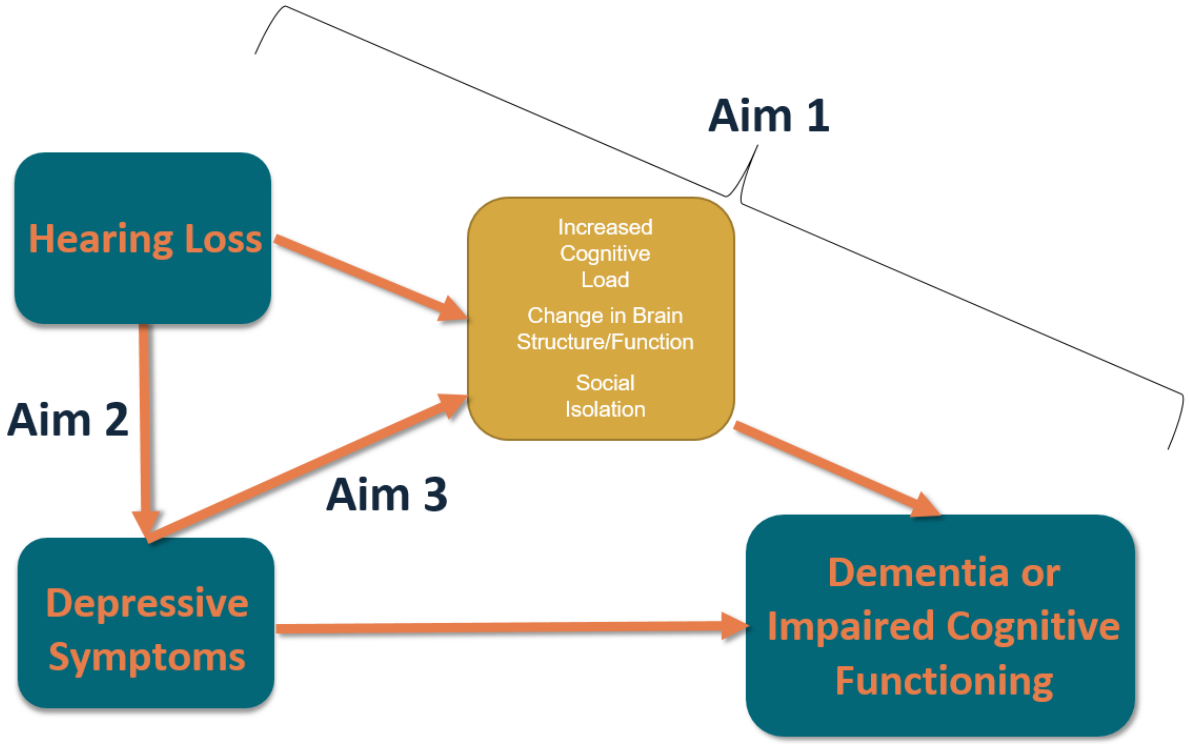


FIGURE 3. A) Peripheral hearing system including the pinna, ear canal, tympanic membrane, ossicles and cochlea. B) Central hearing system incorporating the auditory nerve, parts of the brain stem and auditory cortex

FIGURE 1.4 Conceptual Framework



CHAPTER 2: Hearing and Cognition in an Aging World

Abstract

With the increasing number of older adults around the world, the overall number of dementia cases is expected to rise dramatically in the next 40 years. In 2020, nearly 6 million individuals in the U.S. were living with Alzheimer's disease, the most common type of dementia, with anticipated growth to nearly 14 million by year 2050. This increasing prevalence, coupled with high societal burden, makes prevention and intervention of dementia a medical and public health priority. As clinicians and researchers, we will continue to see more individuals with hearing loss with other comorbidities including dementia. Epidemiologic evidence suggests an association between hearing loss and increased risk of dementia, presenting opportunity for targeted intervention for hearing loss to play a fundamental role in dementia prevention. In this discussion, we summarize current research on the association between hearing loss and dementia and review potential casual mechanisms behind the association (e.g. sensory-deprivation hypothesis, information-degradation hypothesis, common cause). We emphasize key areas of research which might best inform our investigation of this potential casual association. These selected research priorities include examination of the causal mechanism, measurement of co-existing hearing loss and cognitive impairment, and potential of aural rehabilitation. Addressing these research gaps and how results are then translated for clinical use is paramount for dementia prevention and overall health of older adults.

2.1 Introduction

In both the initial 2017 and updated 2020 Lancet Commission reports on dementia prevention[1-2], hearing loss was identified as the leading potentially modifiable risk factor for dementia. A sharp increase in research on the association between hearing loss and dementia has developed over the past decade, building upon initial research from decades ago. As early as 1968, in an experimental condition designed to mimic hearing loss and decreased speech intelligibility, participants demonstrated increased difficulty of performance on word-recall cognitive tasks compared to normal listening conditions[3]. Some twenty years later, a landmark case-control study[4] reported higher odds of dementia in those with hearing loss compared to normal hearing.

Given the rapidly aging population, the global pace of research has accelerated with regards to potentially modifiable risk factors of dementia, including hearing loss. While there is a growing body of knowledge on the association of hearing loss with dementia, significant gaps remain in our understanding. In this article, we aim to (1) provide a foundational understanding of dementia epidemiology, presentation, and diagnosis in the United States; (2) contextualize research on the association between hearing loss and dementia to guide dementia prevention and intervention; (3) review mechanistic theories about the hearing-dementia association; (4) review priorities for future research; and (5) provide a perspective on how we can utilize current and future evidence to improve patient care. We conclude by offering context as we look toward the

coming decades and posit that targeted collaboration between the auditory science and cognitive science communities may present a unique opportunity to alter the landscape of cognitive aging and dementia care.

2.2 Epidemiology and Clinical Diagnosis of Dementia

In its 2020 updated report, the Lancet Commission estimated up to 40% of dementia cases could, in theory, be prevented through intervention on modifiable dementia risk factors[2]. These risk factors include lower educational attainment, hypertension, smoking, obesity, depression, physical inactivity, diabetes, infrequent social contact, excessive alcohol consumption, head injury, air pollution, and notably, *hearing impairment*. Among these modifiable risk factors, it was estimated that intervention on hearing impairment could prevent or delay up to 8% of dementia cases. The disproportionate weight attributed to hearing loss is due, in part, to the high prevalence of hearing loss in the older adult population. It is estimated that two-thirds of adults over the age of 70 years have bilateral hearing loss, with significant growth in the population prevalence of hearing loss expected in the coming decades as the population ages[5-7] (**Figure 2.1**). In addition to its high prevalence, hearing loss has a strong relationship with dementia. Hearing impairment is associated with an estimated 94% increase in risk of dementia over time[1] compared to non-hearing impaired. We provide a population-based perspective and review of the evidence leading to this high level of risk and discussion of the potential mechanism behind this risk in the coming sections. To understand where auditory science may fit into the broader

picture of dementia prevention, we must first understand the role and presentation of dementia within the U.S. population.

2.2.1 The Prevalence and Cost of Dementia

By 2034, the population over the age of 65 years in the U.S. is projected to outnumber those under the age of 19 years for the first time in U.S. history[8]. Moreover, by 2060 the number of individuals over the age of 65 will almost double from 49 million in 2016 to over 94 million[8]. In the U.S., an estimated 5.8 million individuals were living with Alzheimer's disease in 2020, which is expected to increase to nearly 14 million by 2050[5]. The growing prevalence of dementia translates to increased financial, social, and emotional burdens on both communities and families. The total cost of care for those over 65 years living with dementia in the U.S. is estimated at $305 billion in the year 2020 alone[5]. Family and social care accounts for up to 85% of the cost of care for those with dementia[1]. In 2019, 16 million family members in the U.S. provided over 18.6 billion hours of care to individuals with Alzheimer's disease, a labor cost valued at $244 billion[5] – cost that often goes unrecognized. These numbers do little to express the social and emotional strain on individuals and families who are providing or requiring care. The astronomical financial and emotional costs of dementia are among the many drivers behind the research for prevention or intervention at all stages of cognitive aging.

2.2.2 Identifying Dementia

Cognitive decline may be thought of as a trajectory along a continuum spanning normal cognition, expected cognitive changes observed with aging,

mild cognitive impairment (MCI), and dementia **(Figure 2.2)**. Cognitive decline then represents a change in cognitive functioning from an individual's prior ability[9]. While a general decrease in cognitive performance is anticipated with increasing age for many cognitive processes, particularly processing speed and memory[10], departures from prior ability greater than that expected for an individual's age and education suggests possible transition along the clinical spectrum.

Broadly, mild cognitive impairment refers to a symptomatic predementia phase in which the cognitive impairment demonstrated is beyond that expected based on age, education history or other individual characteristics[11]. A formal diagnosis of MCI is made via clinical, cognitive, and functional observed criteria[11]. MCI is considered if concern over a change in cognition from previous ability is expressed from the individual, informant, or clinician, and if cognitive performance is poorer in one or more cognitive domains (e.g., memory, executive function, attention, language, and visuospatial skills) compared to that expected based on age and educational background. With MCI, while difficulty may exist performing complex tasks, the individual can maintain independence with everyday functional activities or requires minimal assistance for social or occupational functioning[9,11]. The diagnosis progresses to dementia when the symptoms of cognitive impairment begin to interfere with the individual's independence in everyday activities[12]. Of paramount importance to understanding research challenges of dementia is the generally insidious progression of disease and clinical presentation. For example, Alzheimer's

disease and related dementias (ADRD) are generally slow and progressive disorders without a definitive onset or clear transition points between an asymptomatic phase, symptomatic predementia phase, and the transition to dementia[12]. Importantly, defined cut-points between age-expected cognitive ability, MCI, and dementia currently do not exist. Therefore, diagnoses are made based on clinical expertise and judgement and may be supported by pathophysiology (e.g., labs, imaging) if available[13]. Readers may seek additional information elsewhere for the distinctions between clinical based dementia diagnosis and diagnosis in research studies which follow a different framework for diagnosis recommendations[11-14].

Clinical diagnosis of dementia is made by a careful history and physical exam, cognitive testing, laboratory, and imaging studies. Neurocognitive evaluations are instrumental components in a provider's clinical examination of a patient's cognitive status. As such, an abundance of neurocognitive tests exist to inform clinical judgement. The assessments evaluate global cognitive performance or cognitive ability within five recognized cognitive domains: memory, attention, executive function, language, and visuospatial. This variety of available cognitive tests are completed across visual and auditory modalities, including some designed to be administered over the phone.

In contrast to the criteria for clinical diagnosis described above, recommendations for criteria for diagnosis in a research setting allow for the additional incorporation of biomarkers. Biomarkers are loosely categorized as those reflecting amyloid-beta deposition, tau deposition, or signs of neuronal

injury11,13-14. Importantly, the biomarkers within each category are not necessarily specific to Alzheimer's disease (AD) and may be indicative of AD as well as other dementia etiology. In research regarding preclinical dementia, biomarkers are used to identify participants with AD pathophysiology with emphasis placed on the hypothesized ordering to biomarker presentation14. However, in MCI or AD related research, usage of biomarkers for diagnosis is more conservative due to an expressed need for additional outcomes research13. While biomarkers suggesting amyloid pathology are thought to precede neuronal injury in research settings, much remains to determine how biomarkers may be used to determine dementia etiology and prognostication, or their utility in short vs long term dementia trajectories before widespread use in clinical diagnosis11. The variety of diagnostic criteria across phase of dementia progression within clinical versus research setting presents challenges to summarizations and inference of this research.

Alzheimer's disease is recognized as the most common type of dementia[5], but increasing evidence recognizes that many older adults demonstrating cognitive impairment have mixed pathology[15]. Other types of dementia such as vascular dementia, dementia with Lewy bodies, and frontotemporal dementia should also be recognized and represent different etiology. While biomarker testing for AD (e.g., amyloid-PET, CSF amyloid-beta and tau) is not required, if available it increases the certainty that the dementia is due to the AD pathophysiological process versus other dementias and could aid in disease and symptom management[12]. At this time, amyloid-PET is approved by the FDA, and

there are on-going studies to examine its utility[16]. Some biomarkers that are thought to be characteristic of AD may also be seen in other dementias. The last few decades have informed our understanding of progression of dementia pathophysiology and the connection to disease stage and the pathophysiologic process. However, as noted, a biomarker-based diagnosis is currently only supported for research-based diagnosis[13] and remains to be clarified for clinical use[12].

As discussed, current evidence suggests a pre-clinical asymptomatic phase may be years if not decades for some individuals[13,17]. A long pre-clinical phase of disease presents challenges for epidemiologic studies and interventions or trials for dementia, yet provides opportunity for early detection and potential prevention of clinical symptom progression. Further clouding the diagnostic picture, not all individuals who demonstrate the neuropathological hallmarks of AD with amyloid beta accumulation and tau protein will develop clinical symptoms (i.e., cognitive decline or functional impairment) during their lifetime. Alternatively, some individuals may demonstrate significant cognitive impairment early with fewer pathologic changes[14,18]. The imperfect relationship between pathological changes and the presentation of symptoms opens questions of what contributes to this varied presentation of disease, and makes clinical prediction for the progression of disease challenging.

2.3.3 Dementia Prevention

What remains clear is that the expected growth in dementia cases worldwide requires action on dementia prevention and intervention as currently

there is no FDA approved disease modifying treatment for ADRD. Current treatment considerations for most forms of dementia have the goal of delaying or minimizing the impact of clinical symptoms for a period of time[2]. In the absence of a cure, the primary objective of epidemiologic research is to identify dementia risk factors associated with pathologic progression or dementia diagnosis, or identify factors associated with the progression of dementia symptoms. Subsequent goals of this research are to then identify opportunities to prevent or postpone dementia along the continuum. With identification of such risk factors, we may then emphasize research on the implementation and delaying of dementia onset, which could have great implications at the population level. An intervention which could delay the onset of dementia by 5 years could lead to a 57% reduction in the number of patients with dementia[14] and 40% lower cost by 2050[19]. With foundational evidence of the association between hearing impairment and dementia from epidemiologic research, the expertise and potential collaboration between auditory scientists and disciplines involved with cognitive aging may enrich our evidence base and contribute towards prevention and intervention efforts.

2.3 The Link between Hearing and Dementia– What We Know Now

In this review, we will primarily highlight evidence of the association and potential causal effect within studies with completed objective measures of auditory function. Self-reported hearing is important, but also incorporates an individual's perception of their hearing and communication ability (i.e. communication demands, regular listening environments, mental health).

Significant heterogeneity in study methodology and study design exists, making comparisons and data synthesis across studies challenging. Prior work has varied in audiometric parameters to define hearing loss, auditory frequencies used, sample size, study population, consideration of potential confounders, and how dementia was measured and operationalized, to name a few. Differing ways of measuring cognitive impairment or dementia are particularly challenging as different criteria may be used across studies. Dementia ascertainment in studies through medical chart history compared to clinical, research-based settings, or in-person dementia diagnosis may introduce variability in dementia diagnosis across studies. Therefore cognitive function may be assessed in a variety of formats depending on the clinical or research environment. A wide variety of additional neurocognitive tests and test batteries across cognitive domains exist[20], in addition to global cognitive screeners (i.e., Mini-Mental State Exam ([MMSE][21]) or the Montreal Cognitive Assessment ([MoCA][22])), to aid in evaluation of cognitive function. These test batteries are often comprehensive, requiring additional time considerations as well as implementation by trained personnel experienced in the delivery of neurocognitive assessments in both clinical and research settings.

2.3.1 Peripheral Hearing Loss

A handful of previous reviews have provided summaries of current evidence on the hearing-dementia association[23-27]. In perhaps the most rigorous review to date, The *Lancet* Commission[1] reported a pooled relative risk from three longitudinal studies[7,28-29] which indicated 1.9 times greater risk of incident

dementia among hearing impaired individuals 55 years of age and older compared to those with normal hearing. The Commission found only these three studies on the association between peripheral hearing impairment and incident dementia met the specified inclusion criteria of: audiometrically (objective) measured hearing, longitudinal evaluation (at least 5 years), and covariate adjustment. Each of these criteria are fundamental components toward investigation of causality. Objectively measured hearing is important when attempting to isolate the independent effect of hearing loss due to cochlear damage on dementia. Cross-sectional evaluations, where hearing and cognition are measured at the same time point, present challenges for causal inference of cognitive impairment. With cross-sectional studies, we are not able to assess which comes first – hearing loss or dementia. Additionally, cognition is particularly susceptible to confounding by psychosocial factors (i.e., episodic depression, anxiety, stress, exhaustion, comorbid conditions, or medications) when measured at one time point but is less susceptible with longitudinal measures. Therefore, comparing group differences in cognitive test scores cross-sectionally may not accurately depict changes in underlying cognitive function but may instead include the effect of these other psychosocial factors. Additionally, many prior studies failed to account for known additional factors (i.e., confounders) which could contribute toward, and therefore cloud, the estimated association found between hearing and cognition.

Other reviews have also reported associations between hearing and dementia. A meta-analysis[24] of prospective studies found 1.22 (95% CI: 1.09,

1.36) or 1.28 (95% CI: 1.02, 1.59) greater odds of cognitive impairment or dementia, respectively, for those with age-related hearing loss. In addition, hearing loss has been specifically associated with declines in global cognitive function, executive function, processing speed, and memory[7,24]. However, what constitutes hearing ability or impairment often differs across studies. Some studies have considered hearing continuously per decibels in hearing level (dB HL), while others have categorized hearing ability (i.e., mild or greater loss, moderate or greater loss, or clinically recognized categories, (WHO Grades of hearing)). This heterogeneity of definitions presents challenges for pooling or summarizing results across studies. The degree of hearing difficulty varies by categorization used and represents different levels of impairment and functional ability such as in categorization of those with any measured hearing impairment (i.e., Pure Tone Average [PTA] ≥25 dB HL) vs. those with a moderate or greater hearing impairment (PTA > 40 dB HL)[30].

Many studies summarize peripheral hearing acuity as a four-frequency pure tone average (PTA, 500-4000 Hz). While this is informative and sufficient for many hypothesis considering functional performance of hearing acuity, when reviewing the potential biological or physiological causal association between hearing and dementia, it may also be worth considering specific frequency ranges depending on the research hypothesis. Additional heterogeneity in study definitions of hearing impairment includes “better” vs. “worse ear PTA.” Studies examining the association of hearing loss and its possible consequences (e.g., hearing loss is the exposure) may wish to conservatively use “better ear PTA,” as

many of the proposed mechanistic pathways underlying these relationships have to do with an individual's overall hearing ability. In comparison, for studies examining biological mechanism and etiology of hearing loss (i.e., hearing loss is the outcome of interest), it may be more informative to consider worse ear PTA.

2.3.2 Central Auditory Function

While an association between age-related peripheral hearing loss and dementia is well established[2], the relationship between cognitive decline/dementia and central auditory function remains much more abstract. Termed *cognitive hearing science* by some[31-32], the interdependence between central auditory function and cognitive processing blurs the distinction between the two processing abilities. Not only does the integrity of an auditory stimulus rely on an accurately encoded signal by a functioning peripheral system, but the stimulus must further be decoded by the central auditory system. This decoding requires the involvement of higher-level cognitive processes. Distinguishing the boundaries between central auditory dysfunction and cognitive impairment has been a subject of research for decades[33-34]. However, as with peripheral hearing loss, studies have used a diverse grouping of definitions, tests, cognitive domains, and sample populations (e.g., both young and old or hearing impaired and non-impaired populations). This heterogeneous operationalization of both processing abilities creates significant barriers to pooled evidence and causal inference on the hearing-dementia association.

Dryden et al. systematically reviewed evidence in 2017. While the quality and potential bias in the studies included were mixed, among studies involving

adult unaided listeners with normal to moderate hearing loss, a correlation between cognitive performance and speech perception was overall weak depending on the speech-in-noise test used and cognitive domain of interest, with the greatest correlation seen with processing speed. The degree un-aided hearing loss plays in moderating the relationship between central auditory functioning (e.g., decoding of speech stimuli or speech perception ability in noise) and cognitive performance remains to be determined. However, results continue to highlight the interdependence of cortical resources utilized during both central auditory processing and cognitive processes[35-37].

The interdependence between central auditory function and cognitive processing presents challenges to inference but also unique opportunities in identifying targets for prevention. Prior work has hypothesized that central auditory dysfunction (CAD) may be a prodromal symptom and therefore an early marker of cognitive decline in older adults[38]. AD pathology is known to reach the primary auditory cortex. Work conducted nearly 30 years ago demonstrated AD pathology of plaques and neurofibrillary tangles within the medial geniculate body and central nucleus of the inferior colliculus as well as the primary auditory and auditory association cortices of patients diagnosed with AD, but not in non-AD elderly patients[39]. Braak staging[40] indicates that auditory association cortices are one of the last brain regions affected by AD pathology, supporting central auditory dysfunction as a marker of AD, but with unclear indication of CAD as an *early* marker. In a volunteer sample from a dementia surveillance cohort[41], the hazard ratio for incident dementia was 9.9 (95% CI: 3.6, 26.7) among those with

severe central auditory dysfunction, as measured using the Dichotic Sentence Identification test, compared to those demonstrating normal central auditory function. Further work suggested that the Dichotic Sentence Identification test in free report mode may be the most sensitive test for the presence of memory impairment among those demonstrating mild memory impairment without dementia[42]. Investigation of the association between central auditory processing and biomarkers for AD neurodegeneration including CSF tau, cortical thickness and volumetric measures of AD-related brain regions was consistent across measures of central auditory processing[43]. Whether CAD has utility for predicting dementia in addition to predictions possible with current ADRD biomarkers has yet to be determined.

The nature of the association between central auditory function, as measured via speech-in-noise ability, and cognition may differ by aided vs. unaided hearing. Additional work has demonstrated that for aided listening with background noise, higher level cognitive processing capacity was the most important factor in the differences observed in speech understanding performance. In contrast, for unaided listening, peripheral hearing was the predominant factor driving performance. For select individuals, high frequency hearing played a predominant role regardless of aided status or degree of loss[35].

Some researchers have described an idea of *central presbycusis* meant to represent “age-related auditory processing disorder underlying poor speech understanding in noise, competing speech, or distorted speech”[44]. The existing research on this construct is heterogeneous, incorporating measures of both

speech and non-speech stimuli. A review of past research[45] concluded insufficient evidence existed to claim *central presbycusis* as an independent construct, but proposed that it may instead represent a disease manifestation from multiple conditions involving age-related or disease-related changes in both the auditory system and the brain.

2.3.3 Management of hearing loss for dementia prevention

As mentioned, the treatment of hearing loss makes it a worthy target of interest among dementia risk factors due to the readily available management strategies for hearing loss (e.g. hearing aids). The data on the use of hearing aids to decrease risk of cognitive decline in observational or cross-sectional studies are mixed[46-49]. In observational studies, we are often not able to control factors which influence if someone becomes a hearing aid user (e.g., higher education, higher socioeconomic status, greater access to healthcare), many of which are also factors which are protective against dementia. Therefore, it is challenging to disentangle the potential effects of hearing aids on cognition versus the effect of these other factors, possibly influencing the effect seen and therefore introducing bias into our study. However, the question of whether hearing aid use or other treatments for hearing impairment may alter the subsequent risk of dementia has begun to receive attention in well-designed pilot studies and clinical trials. These clinical trials aid in minimizing this potential bias through study design tools such as randomization and masking[50]. The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) pilot study conducted in 40 older adults demonstrated clear efficacy in hearing handicap and social

outcomes and a suggestion of efficacy in improving or stabilizing memory scores (although not powered to detect a difference) for those randomized to the use of a hearing aid compared to a successful aging education control[51]. A full-scale (N=977) randomized clinical trial is currently being conducted[52]. A pilot study of hearing aid use by older adults with depression, another possible downstream risk of hearing impairment which may mediate or moderate the hearing-dementia association, observed small to moderate improvement in depressive symptoms, memory, and general cognitive functioning[53]. Further, consideration of the age and rapidity of hearing loss onset and its proximity to hearing aid uptake, and the influence of other rehabilitation strategies on dementia risk is vastly understudied.

Several studies have begun to investigate cognitive function among cochlear implant recipients following surgery. Work in a pilot sample among 23 cochlear implant candidates and 16 implant recipients demonstrated better performance on measures of reaction time, cognitive flexibility, working memory and strategy use compared to implant candidates[54]. Prospective evaluation of cognitive performance among individuals pre and post cochlear implant surgery has suggested improved cognitive performance on global cognition or executive function post implantation[55-56]. However, many studies have focused on pre/post performance on speech perception, perceived function, and quality of life for older adults rather than neurocognitive outcomes specifically. While these outcomes are absolutely important, investigation of the impact on cognitive performance following cochlear implant surgery using neurocognitive

assessments in multivariate models with appropriately considered control groups are limited[57-58]. With expanding cochlear implant candidacy and our aging population, well designed longitudinal studies could vastly improve our understanding and counseling considerations for older adult cochlear implant candidates.

2.4 Mechanistic Theories

As described above, the association between central auditory function and dementia is complex and its interdependence with dementia presents challenges for causal inference. Therefore, current mechanistic theories predominantly consider peripheral hearing impairment as a potential cause of dementia and central auditory function as a marker of cognitive decline. While there are gaps in the understanding of mechanism(s) behind the relationship between age-related hearing loss and dementia, elucidating these mechanisms is vital for the design, implementation, and evaluation of preventive strategies, interventions or recommendations for patient care or health policy. Hypotheses on the causal mechanism of the association have eloquently been described in prior works[59-61]. While limited evidence supports the notion that dementia leads to hearing loss[33,62] the direction of the association between age-related hearing loss and dementia remains to be clarified. A greater body of evidence supports how age-related hearing loss may contribute to cognitive decline directly ("sensory-deprivation" hypothesis) or indirectly ("information-degradation" hypothesis), or how both may be the result of an external variable all together ("common-cause" hypothesis)[61]. We will briefly review evidence for each of these mechanistic

theories as depicted in our modified mechanistic framework (**Figure 2.3**). Readers may seek additional evidence for each proposed hypothesis in Wayne & Johnsrude (2015) or Lin et al. (2014b).

2.4.1 Sensory Deprivation Hypothesis

Evidence suggests that prolonged sensory deprivation due to age-related hearing loss has a lasting adverse effect on brain structure and function. Age-related hearing loss could lead to cortical re-allocation, de-afferentation, or atrophy to support speech perception processing. This reorganization can be to the detriment of general cognitive performance, adding to existing brain pathology (e.g., amyloid burden, neuronal loss) by altering critical brain regions which could otherwise be utilized for higher-level cognitive processing. Prolonged sensory deprivation from peripheral hearing loss may lead to changes and decreases in cortical brain volume similar to that seen with cognitive decline[63-64]. In particular, changes to temporal lobe volume and reduced gray matter density have been noted in those with peripheral hearing loss[59, 65-66]. These are brain regions important for semantic memory and involved in progression along the dementia continuum. Brain regions affected include the superior temporal gyrus and Heschel's gyrus as well as frontal and pre-frontal brain regions[67]. Reduced whole-brain gray matter volume is significantly associated with brain regions recruited for speech understanding, including the frontal cortex and hippocampus[68]. Evidence indicates hearing loss is associated with lower white matter microstructural integrity in brain regions critical for cognitive processing, even in older adults considered dementia-free[65,69-71].

Critical ages or length of sensory deprivation necessary to evoke these structural changes remains to be characterized. Even in early stages of cognitive impairment, cortical reorganization due to age-related hearing loss is apparent[72-73], however the degree of reorganization necessary to evoke brain atrophy and changes to cognitive performance has not been determined. This research suggests prolonged sensory deprivation may lead to a reduction in cortical volume beyond that seen from dementia pathology alone or may necessitate reorganization due to prolonged deprivation. This additional structural and functional decline results in further restriction of cortical capacity available for cognitive processing.

2.4.2 Information Degradation Hypothesis

In contrast to the physical nature of the association between age-related hearing loss and cognitive decline posed by the sensory deprivation hypothesis, the information degradation hypothesis proposes that the association is due to the increased cognitive processing required to compensate for an impoverished sensory input. This increased processing for degraded perception draws on the same resources needed for other higher-level cognitive processing and semantic encoding[74]. The subsequent increased cognitive demands required to accurately encode information takes extensive listening effort with particular demands on attention, memory, and executive function[74-77]. The cognitive capacity of an individual and ability to compensate for decreased cognitive performance varies and may partially explain some of the variance between existing brain pathology and presentation of clinical symptoms as previously described. This listening

effort required with hearing impairment may increase the cognitive load and the full demands placed on the brain at any time[78]. These demands then draw on the compensatory buffering ability of the individual, potentially resulting in the earlier presentation of clinical symptoms and dementia.

Additionally, differences between compensatory mechanisms activated for cognitive performance between older and younger adults with sensory deficits is evident and may highlight increased fatigue in older adults for the dual tasks of listening and understanding[79]. Thus, this hypothesis implies temporary cognitive impairment. Through the amelioration of auditory input, cognitive performance on higher-level tasks might be restored.

2.4.3 Common Cause

The association between hearing and cognition in older adults could also simply stem from the same underlying mechanism, resulting in both impairments[61-62]. Investigation of a common cause associated with both hearing and cognitive impairment has been primarily evaluated through PTA due to the presumed independent effect of peripheral hearing. General neural degeneration commonly seen with aging could potentially result in decreased cognitive function and auditory performance[61,80]. Age associated slowing of processing speed may result in slower overall cognitive functioning as well as slower processing for sensory integration and perception[10,33]. Concurrent changes in both cognitive and sensory modalities in older adults could also stem from conditions such as cerebrovascular disease[1,81-82]. Systemic vascular pathology impacting the spiral ganglion or stria vascularis as well as the vasculature of the brain could

potentially alter both auditory and neural functioning. Investigation into an underlying common genetic risk between AD and hearing loss suggests genetic risk for AD (as represented by a weighted sum of identified polymorphisms for AD and the inflammatory pathway) is associated with poorer speech-in-noise performance and self-reported difficulty hearing with background noise[83]. However, question of causality in this association between shared genes remains[84] as the number of studies investigating genetic risk are limited, warranting further investigation.

2.4.4 Other Potential Factors in the Association between Hearing and Cognition

The association of hearing and cognition may also be mediated through other potential risk factors for dementia, including social isolation, depression, or decreased physical activity. Social isolation and loneliness as a consequence of hearing loss is not a new concept, nor is the idea that decreased social interaction increases risk of dementia[85-88]. While evidence is mixed, hearing loss may lead to increased risk of depression in older adults, which has been considered either a prodromal symptom or an independent risk factor for cognitive decline (see also for review Rutherford et al 2018). Further, hearing loss may lead to reduced physical activity due to anxiety from decreased auditory awareness[89-90]. Additional work suggests hearing loss is associated with increased prevalence of frailty among older adults which has been suggested to increase risk for dementia[91-92]. How these potential mediators fit within the larger

context of the above hypothesis remains to be clarified, yet each offers opportunity for targeted intervention.

2.4.5 Summary of Proposed Hypotheses and Mechanisms

It is likely that one or more of the proposed mechanisms explain and/or mediate the association between hearing loss and dementia. The specific contribution of each proposed mechanism toward risk of dementia may vary individually. While common risk factors (i.e., age, education, vascular disease) are thought to contribute towards the association[35,61,93], these factors likely do not explain the full story. In epidemiologic studies which have attempted to control for these confounding factors as best as able, the association persists, potentially indicating that other mechanisms are likely involved.

2.5 Priorities for Future Research

Given the wide multi-disciplinary scope of research on hearing and dementia, identification of research priorities can help propel the field of auditory science toward meaningful advances in both hearing and dementia care. A foundational objective is identifying subgroups of individuals who may be at a greater risk of cognitive decline or may benefit most from intervention. Many crucial research questions and additional perspectives exist [Wayne & Johnsrude (2015), Whitson et al (2018)]. Here we highlight three areas of research priorities which we believe will provide the greatest advancements in understanding the association and possible causal role of hearing impairment along the dementia continuum. These include: 1) the driving mechanism behind the association, 2)

standardized use of validated measurement tools for the assessment of hearing and cognition in older adults, and 3) evaluating the efficacy/effectiveness of interventions to treat hearing impairment to delay the onset of dementia (**Figure 2.4**).

2.5.1 What is the driving mechanism behind the hearing-cognition association?

If we can determine the link(s) or driver(s) behind the association of hearing loss with cognition, we may better plan for and provide appropriate intervention options to delay the onset or alter the trajectory of the clinical course of dementia. How best to intervene, and ultimately whether treatment for hearing loss will be effective in decreasing or delaying dementia risk, largely depends on the underlying mechanism. Research has yet to determine if there is an independent effect of hearing loss on cognitive impairment for older adults. As described above, the relationship between AD pathology and the presentation of symptoms is heterogeneous. We do not yet know by what means hearing impairment may influence a potential buffer which delays/prevents the presentation of symptoms in some individuals yet leads to earlier symptomatology in others.

If the association between hearing impairment and dementia was only due to a common cause of both hearing loss and dementia, such as vascular disease or genetics, the opportunity for directly preventing or changing the progression of dementia through treating hearing loss would be limited. In turn, research focus would shift to intervention on the underlying biological or neurological mechanism

at hand which could have significant downstream effects on hearing and cognition for older adults.

Both the sensory-deprivation and information degradation hypotheses imply a more direct effect of hearing impairment on dementia risk. While the long-term vs short-term timeline of this effect varies by hypothesis, both suggest that hearing impairment leads to downstream effects on available cognitive resources. However, the nature of the effect from either hypothesis has implications for approaches to intervention. With structural and functional changes in the brain due to hearing impairment via the sensory deprivation hypothesis, early identification of hearing impairment and options to potentially delay or prevent deafferentation or atrophy within the auditory or sensory regions of the brain are essential to prevent lasting structural damage. This hypothesis may further demonstrate treatment benefit at later stages of hearing impairment, for example, by delaying additional neural reorganization or atrophy. In contrast, the information degradation hypothesis would provide a strong argument for new and existing hearing intervention options at any stage of the disease process—with improved integrity of auditory input via rehabilitation or hearing treatment, the strain on cognitive resources for environmental awareness or communication would be reduced.

Disentangling central auditory dysfunction and cognitive decline will be essential for targeting prevention efforts or early identification of subgroups at greater risk for cognitive decline. The temporality of the association and whether central auditory dysfunction is an early marker of dementia or represents an

independent process, and how to differentiate the two, remains a challenge in understanding the link between hearing loss and dementia. The dependence of both peripheral and central hearing on higher-level, auditory-based cognitive functioning leaves significant questions of how to interpret the influence of each component along the auditory pathway. If central auditory dysfunction represents an early marker of dementia, how measures of CAD may fit within the context of existing early biomarkers of dementia or neuropsychiatric test batteries remains to be determined.

In all likelihood, multiple mechanisms are involved in the hearing-dementia association; thus, further investigation should determine if one mechanism serves as a primary driver and how each might interact to alter risk. It is possible the primary driver is unique to the individual, allowing for a person-centered approach to intervention that alters the progression to dementia.

2.5.2 How do we best measure hearing and dementia in this process?

Data are only as good as the measurement tools used to collect them. If we are not able to effectively measure our construct of interest, then our data may not appropriately answer the question of interest. The majority of studies on hearing impairment and dementia or cognitive decline have focused on utilizing audiometry or self-reported hearing – yet these measures reflect two differing constructs for hearing impairment. While both measures reflect aspects of hearing function, understanding the primary research objective will determine the most effective measure. We need to identify what hearing measures (i.e., self-reported hearing, pure tone average, specific configuration of impairment, central

auditory function measures) provide the best representation of the mechanisms driving the association. We should also identify the most practical and useful measure to estimate a causal effect or for detection of cognitive change in a clinical environment or population-based research study. Synthesis and harmonization of data are most effective and informative if less heterogeneous and streamlined types of measures are collected across a wide range of studies and represented populations. Because the auditory pathway encompasses both peripheral and central hearing components, effectively and efficiently discerning and utilizing these respective measures for study of cognition in older adults is imperative to progress in this research.

There is need to disentangle the potential for sensory bias in cognitive testing and the dependence on cognitive functioning for auditory measures, particularly speech-in-noise measures. Cognitive tests and screening tools rely on an individual's auditory or visual ability for completion. This dependence has led some to question if auditory or visual impairments may lead to potential sensory bias with cognitive tests[94-95]. Confirming the validity of the test within the cognitive domain and construct of interest is essential for use in the growing number of older adults with sensory impairments[96]. Among important questions to consider is whether accommodations during testing for individuals with hearing loss is appropriate. Cognitive tests which maintain integrity of the assessment but are simple and efficient for hearing impaired older adults, researchers, and clinicians will have the greatest utility. Addressing hearing and vision needs prior

to cognitive assessments will be important for confidence and synthesis of study results.

2.5.3 Does treating hearing loss alter dementia risk?

Evidence for the impact treating hearing impairment has on cognitive decline or dementia is accumulating. However, until the results of the current longer-term clinical trials are available, the evidence of these effects on cognitive decline and dementia risk largely stem from observational studies. There is great power in our insights gained from observational studies, however evidence of causality for decreased or delayed cognitive decline due to hearing aid use is more challenging. Challenges include selective effects of who chooses to pursue hearing aids as well as heterogeneity in device, fitting, use, temporality, or unmeasured confounding. Not only must we still determine if treating hearing loss using hearing aids attenuates dementia risk or delays presentation, we also have a limited understanding of how and when to best intervene.

Public health prevention strategies recognize the potential for targeted intervention at each stage of the disease process— known as primary, secondary, and tertiary prevention[50] (**Figure 2.5**). Evidence for hearing intervention at these levels of prevention remains limited, and an understanding of how hearing loss treatment throughout the process might influence upstream higher-level cognitive processing is virtually non-existent. Determining the best choices for prevention within a population is dependent on evidence of efficacy, effectiveness, and cost efficiency— all areas with extensive gaps in evidence for hearing loss and dementia.

Primary prevention strategies involve the reduction of risk factors before the disease process begins[50]. In this association, primary prevention focuses on reducing the onset of cognitive decline among those with cognitive abilities with that expected for age and background. Early identification of hearing loss and adoption of hearing treatment may prevent structural changes in the brain (sensory deprivation hypothesis) thereby reducing the additional 'hit' to cortical structures and demands on neural allocation. Key objectives of hearing aid clinical trials are to determine if adoption of hearing aids for hearing impairment (at least peripheral hearing impairment) may delay progression of cognitive decline and how the use of amplification may therefore influence the outcome.

Secondary prevention involves the early detection and prevention of disease through screening and early identification, and encompasses intervention upon those at clear risk of progression of cognitive impairment. Identification of hearing impaired older adults with concurrent mild cognitive impairment, subjective cognitive complaints, or significant biomarkers of dementia are the focus of these efforts. Delay of further cognitive decline and transition to dementia through amplification use, aural rehabilitation and communication strategies would make a lasting contribution to dementia prevention.

The last stage of prevention, tertiary prevention, in this case follows the onset of dementia and focuses on supportive and rehabilitative services to minimize morbidity and mortality or maximize quality of life. The use of hearing aids may decrease risk presented by mediators within the hearing and dementia

pathway by reducing social isolation or depression risk for older adults, which can worsen dementia symptom trajectories. Importantly, neuropsychiatric (i.e. depression, agitation, anxiety, delusions, aggression, apathy etc.) symptoms are fairly common at all stages of dementia and are associated with poor outcomes for both patients and caregivers[97]. However, hearing aid use has been associated with fewer and lower severity neuropsychiatric symptoms and less severe depressive symptoms in older adults with cognitive impairment[98]. Therefore, not only does hearing aid use among ADRD patients demonstrate improved communication, decreased hearing handicap, and improved quality of life[47, 99-100], it may also reduce common dementia-related behaviors detrimental for individuals and challenging for caregivers and providers.

Within tertiary prevention, we must further determine how to provide auditory rehabilitation for adults with cognitive impairment[101]. While current evidence suggests treating hearing loss in cognitively impaired older adults yields benefits as described above, the strength of the evidence is limited due to its case-report and subjective nature. Determining alternative accessible and effective means of hearing rehabilitation for cognitively impaired and aging adults is imperative to meeting future population needs. Even with changes in health policy improving access to hearing care and rehabilitation, hearing aids may not be feasible for some older adults and likely do not meet the listening needs of many adults when used as the only form of rehabilitation. Alternative strategies which present non-technology driven proposals[102] should be evaluated to

determine if these approaches better meet the auditory and cognitive needs for some older adults.

2.6 Utilizing current and future evidence to improve patient care

How auditory scientists, cognitive scientists, epidemiologists, and other investigators present the research on hearing and cognitive impairment can have significant implications for how clinical providers educate patients and their families. Epidemiologic studies comprise much of the research on hearing and cognitive impairment in older adults. These studies are primarily observational, conducted using population-level data. This design allows for the observation of health-related trends within a selected population of individuals. Thus, on average, observation of a significant positive association in epidemiologic data suggests those with hearing impairment demonstrate an increased risk of cognitive impairment compared to those with normal hearing. This type of data does not imply that a given individual with hearing impairment will go on to develop dementia, but helps identify groups of individuals whom primary care providers may wish to monitor for cognitive change.

In comparison, some of the work by cognitive and auditory researchers has been conducted within selective and controlled clinical or research environments. These environments allow for ease of participant recruitment and control of variables, yet the use of clinic-based populations does not necessarily ensure that the complex relationship between hearing ability and cognitive impairment seen within the broader real world is captured. Many clinic- or research-based participants may have underlying concerns which have led them

to participate in studies, and participants often possess characteristics which may not be generalizable or representative of the general population or under-represented groups. Thus, while epidemiologic cohorts also have their limitations, understanding trends within a population helps identify areas of further research. These population trends inform health program planning, health policies, and identification of areas for targeted research. Each research environment presents differing angles or perspectives with which scientists may address research needs, enriching collaborations and our comprehensive approach to the public health issue.

Given the varied disciplines involved in research on hearing and cognitive impairment, understanding how to synthesize the current evidence, translate findings, and guide future research for scientific progression is vital. However, current research has primarily remained siloed within disciplines. Auditory science and cognitive science researchers have the opportunity and expertise to address aspects of the primary research gaps described above. Transparency of and careful consideration of study design, measurement tools implemented, and discussion of results' applicability for clinical or community populations is essential to characterize the role of hearing impairment within the dementia timeline and meet the needs of our current and future older adults.

2.7 Conclusion

While research on the contribution of age-related hearing loss to dementia risk has been around for decades, growing evidence of the adverse consequences of hearing loss for older adults has brought conversations about

hearing health and care into the clinical exam room and to the attention of older adults and policy makers. The human and economic expense of caring for the coming wave of adults reaching or past retirement age demands interdisciplinary collaboration. Auditory science has the opportunity to contribute towards efforts to reduce this impact. Identification of the mechanism(s) driving the association between hearing and dementia, directed hearing-dementia research for the greatest public health impact and societal needs, and thoughtful translation of this research for clinicians and patients can have a monumental impact on prevention and intervention strategies for older adults. The interdependent and synergistic processes of hearing and cognition require careful approach. Optimizing our strategies to treat hearing loss could diminish the risk of adverse outcomes and enhance health and quality of life for older adults.

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FIGURE 2.1 Estimated and Projected Trends in Prevalence of Hearing loss (mild hearing loss and moderate or greater hearing loss) and Dementia in older adults by age categories in the United States from 2020 to 2050.

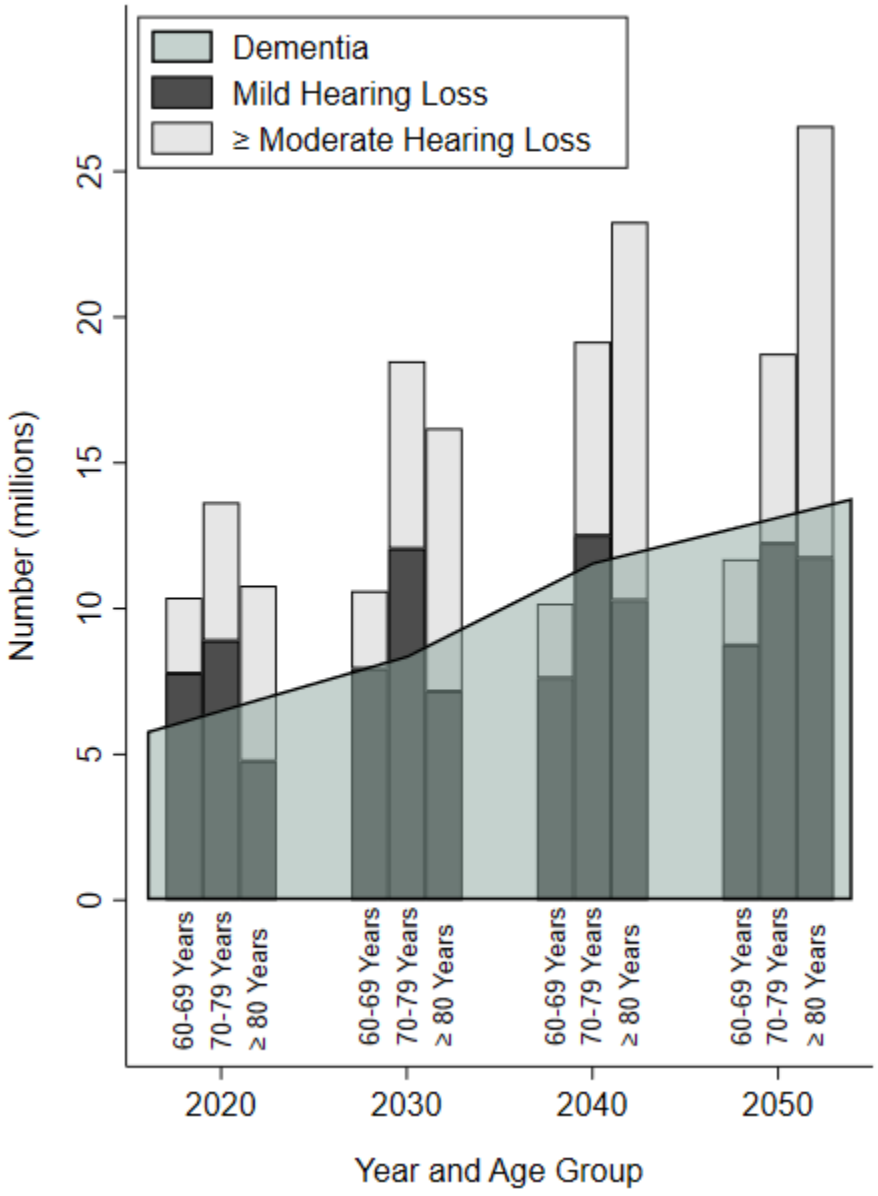

FIGURE 2.1 Data compiled from Goman et al. 2017 and the Alzheimer's Disease Facts and Figures 2020 Report

FIGURE 2.2 Conceptual Model of cognitive trajectory along the cognitive decline dementia continuum.

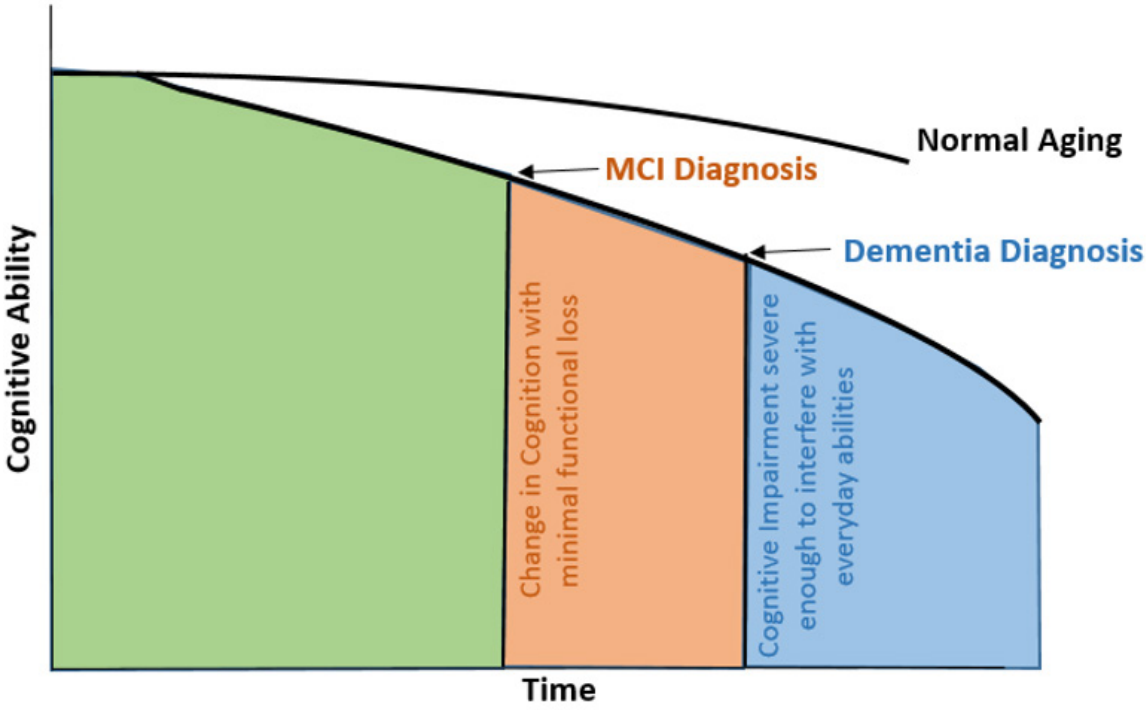

FIGURE 2.2 This continuum represents a departure from normal aging with decreased cognitive ability greater than expected with normal aging (green region). Mild Cognitive Impairment (MCI) diagnosis may be provided with a change in cognition with minimal functional loss (orange region). Dementia diagnosis may be provided with further progression with cognitive impairment severe enough to interfere with every ability (blue region)

FIGURE 2.3 Hypothesized framework for the mechanism of the hearing and dementia association.

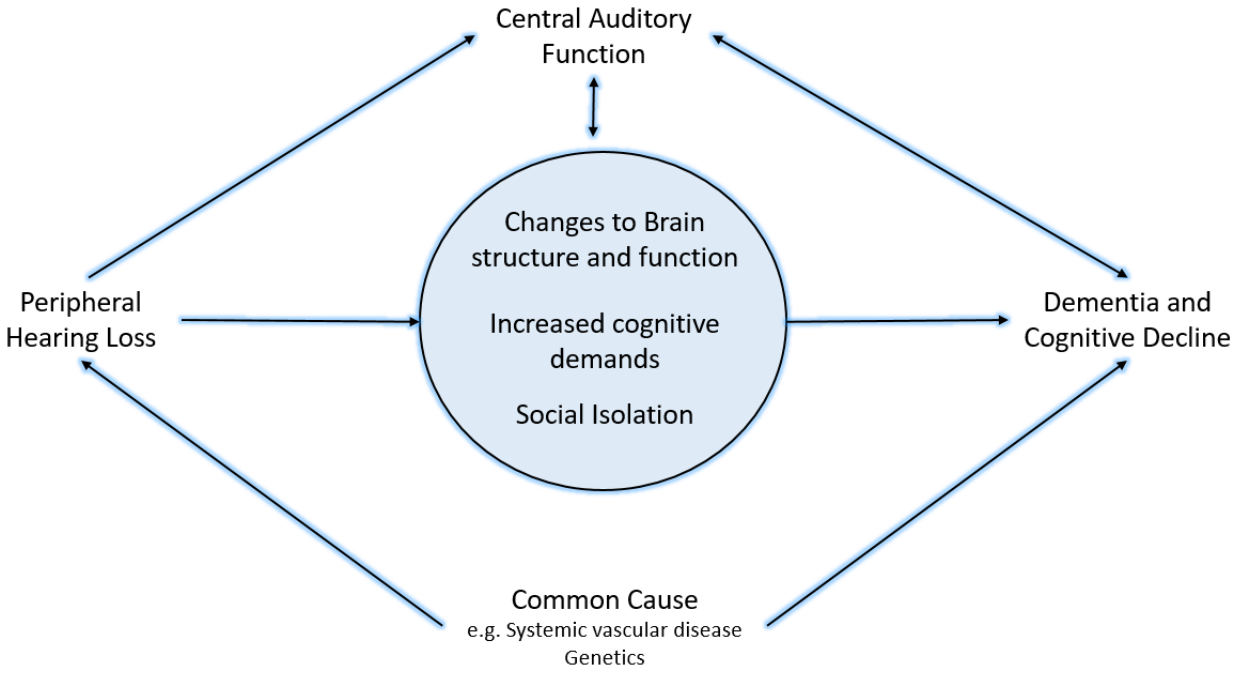

FIGURE 2.3 The center blue circle includes potential causal paths between peripheral hearing loss and cognitive decline or dementia, including changes to brain structure and function (i.e., sensory deprivation hypothesis), increased cognitive demands (i.e., information degradation hypothesis), and other effects such as social isolation. Additionally, a common cause such as systemic vascular disease or genetic factors may lead to both peripheral hearing loss and cognitive decline and dementia. Further inclusion of central auditory function as a result of direct and indirect effects from this causal pathway and may serve as a marker of cognitive decline or dementia. It is likely more than one of the pathways depicted may explain the link between hearing and dementia

FIGURE 2.4 Key Research Gaps in Hearing Impairment and Cognition.

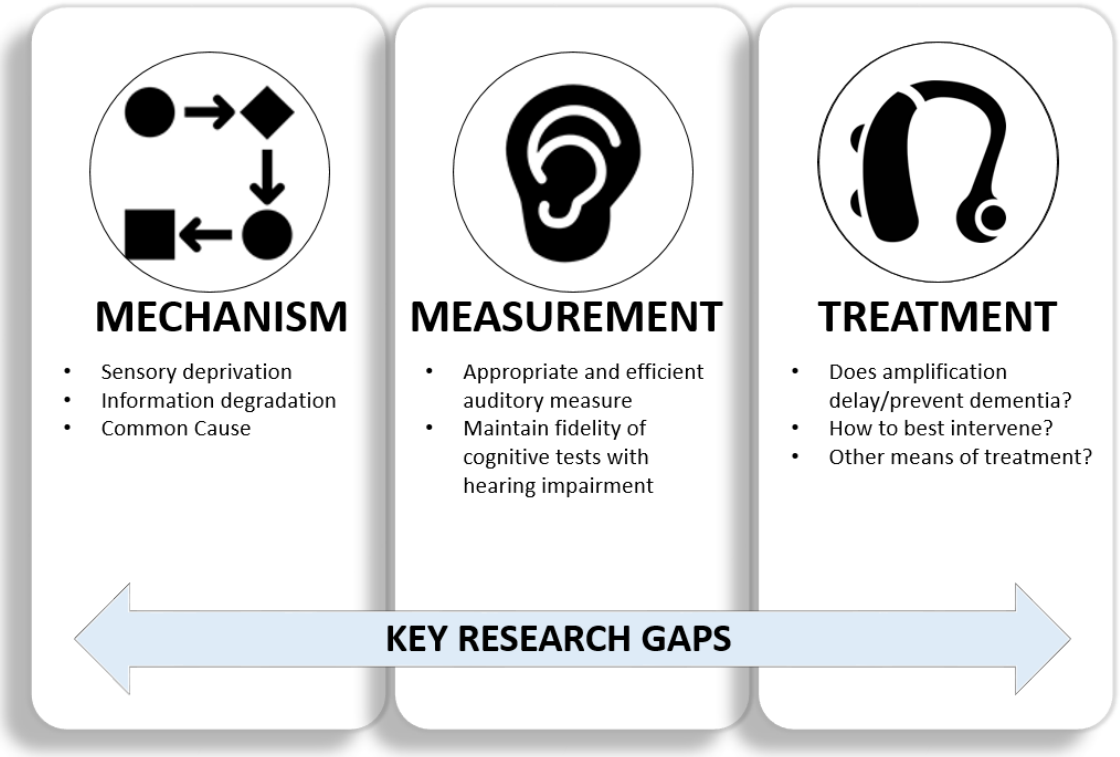

FIGURE 2.4 Targeted research on the mechanism behind the association between hearing and cognition will guide intervention and prevention strategies. Additional research gaps include careful study and identification of the most appropriate and efficient auditory measure for association and causal effect studies of hearing and cognition, as well as ensuring fidelity of cognitive tests with hearing impairment. Further understanding of if treating hearing loss via amplification or another means influences dementia risk is vital for public health

FIGURE 2.5 Schematic of levels for dementia prevention through identification of and management of hearing loss in combination with the cognitive decline continuum.

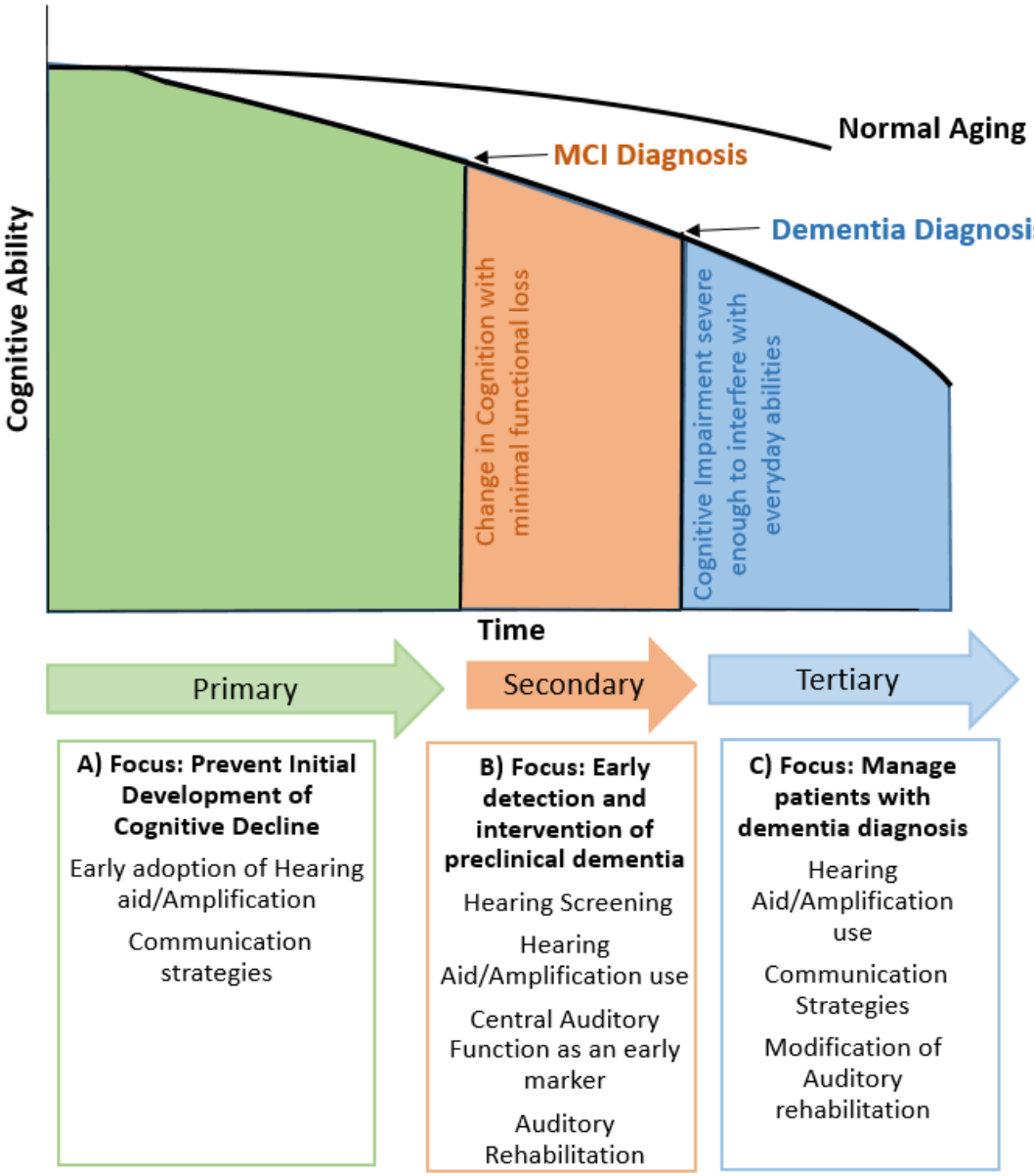

FIGURE 2.5 A) primary prevention focusing on the prevention of initial development of cognitive decline in normal cognitive aging B) secondary prevention focusing on early detection and intervention of preclinical dementia C) tertiary prevention with a focus on management of patients with a dementia diagnosis

CHAPTER 3: Hearing Loss and Risk of Depressive Symptoms in Older Adults in the Health ABC Study

ABSTRACT

Background: Hearing loss (HL) is a highly prevalent condition among older adults and may lead to increased risk of depressive symptoms, yet has received little characterization by race and gender. In both cross-sectional and longitudinal analysis, we quantified the association between HL and depressive symptoms, incorporating the variable nature of depressive symptoms over time.

Methods: Data were from the Health, Aging, and Body Composition (Health ABC) study, a racially diverse cohort of community-dwelling older adults' age 70-79 years. Depressive symptoms was defined using the Center for Epidemiologic Study Depression Scale short form (CES-D 10) and reported use of treatment for depression. Significant depressive symptoms was defined as CES-D 10 score ≥10. Hearing acuity was defined via pure-tone average in decibels hearing level (dB HL) in the better hearing ear at frequencies 500-4000 Hz, categorized as normal hearing (PTA<25 dB HL), mild HL (PTA 25-40 dB HL), and ≥moderate HL (PTA >40 dB HL). Associations between hearing status and baseline depressive symptoms were quantified using logistic regression, with incident depressive symptoms using Cox proportional hazard models, and with change in depressive symptoms over time using generalized mixture models and multinomial logistic regression.

Results: Among 2,089 older adults (1,082 women, 793 Black), 793 had a mild hearing loss and 435 had a moderate or greater HL. At baseline, a moderate or greater HL was associated with greater odds of significant depressive symptoms

(OR: 2.45, 95% CI: 1.33, 145), with notably higher odds among women and Black participants. Higher risk for incident depressive symptoms was observed in the overall sample (HR: 1.26 95% CI: 1.00, 1.58). We identified three depressive symptom trajectory patterns: low, moderate increasing, and borderline high depressive symptom levels from growth mixture models. Moderate or greater HL was more prevalent in the borderline high depressive-symptom trajectory class compared to the low depressive symptom trajectory class (RRR 1.16, 95% CI: 1.01, 1.32). A poorer depressive symptom trajectory was more common among Black participants and less common among White participants, regardless of hearing status.

Conclusion: HL was associated with greater depressive symptom, particularly among women and Black participants. Investigation of psychosocial factors related to this risk and potential amelioration by hearing aid use could have significant benefit for older adults' quality of life.

3.1 INTRODUCTION

Two-thirds of adults over the age of 70 years have a hearing loss, with prevalence rising for each additional decade of life[1]. While traditionally viewed as primarily impacting communication, increasing evidence indicates hearing loss may lead to adverse psychosocial effects, including depression or depressive symptoms[2-4]. Older adults with hearing loss may avoid social situations or have difficulty engaging with surroundings and loved ones due to difficulty communicating in challenging listening situations. Further, changes in brain structure due to hearing loss may lead to increased vulnerability for depressive symptomatology or result in behaviors which can increase social isolation and risk for depression[5]. Recent hypotheses suggest the psychosocial impact of hearing loss may differ not only by environment and listening needs, but also by race and gender[5-7]. With the high prevalence of hearing loss in older adults, understanding how hearing loss influences risk of depression, and potential differences presented across race and gender, may aid in the identification of those at higher risk for late-life depression.

Prior studies have demonstrated a range of associations suggesting hearing loss is independently associated with depressive symptoms in older adults, yet there are discrepancies in previous findings[8-13]. To date, longitudinal evaluations of hearing and depression are limited[9-11]. However, the presence of depressive symptoms is commonly influenced by life events, placing an importance on repeated depression measures. Some evidence suggests

prolonged increased levels of depressive symptoms may further increase risk for cognitive outcomes like dementia. Recent work in the Health, Aging, and Body Composition Study[11] investigated the association of self-reported hearing status on trajectories of depressive symptom change over 10 years. Results suggest baseline impaired hearing was associated with a greater odds of a trajectory of increasing depressive symptomatology and of persistently high depressive symptoms, compared to a group characterized by low depressive symptom trajectories.

The ability to communicate effectively with others includes not only measured hearing ability, but also influences from a person's social, psychosocial, and life circumstances. Therefore, aspects of one's socially defined race and gender may present different influences on risk of depression by hearing status as race and gender additionally include social, socioeconomic and cultural influences. Specifically, among women, prior work has shown women place a greater emphasis on network with friends and family and emotional intimacy than men, actions which have demonstrated protection against depressive symptoms but which may be adversely impacted by hearing loss[14]. Moreover, the psychosocial stress from inclusion in a marginalized group among Black individuals has been well documented[15-17]. This prolonged psychosocial stress has been linked to increased risk for depressive symptoms[17] and may be exacerbated further among hearing impaired Black older adults and might therefore lead to faster or poorer trajectories of symptoms over time.

Our study aims to expand upon prior work with cross-sectional and longitudinal investigation of the association between audiometrically-assessed hearing loss and depressive symptoms, overall and by race and gender. We aim to investigate the degree to which hearing loss is associated with greater prevalence of depressive symptoms, greater incidence of depressive symptoms, or a greater increase in depressive symptoms over time. We leveraged data from the Health, Aging, and Body Composition Study (Health ABC). We hypothesize hearing loss is associated with greater risk for the presence and new occurrence of depressive symptoms, as well as larger changes in severity of depressive symptoms, particularly among women and Black participants.

3.2 METHODS

3.2.1 Study Population

Participants were enrolled in the Health ABC study, a prospective study of 3,075 well-functioning, community-dwelling Black and White older men and women aged 70-79 years recruited in 1997-1998 from Pittsburgh, Pennsylvania and Memphis, Tennessee[18]. Participants were selected for inclusion in this study if they reported no difficulty walking ¼ mile or climbing up 10 steps. Follow-up consisted of yearly clinical examinations and 6-month interim phone calls, terminating in 2013. Audiometry was conducted at the study visit during the 5th year of follow-up. This study was approved by the Institutional Review Boards of all participating institutions.

Participants were excluded if: 1) they did not attend the year 5 clinical visit when audiometric testing was performed (n=779); 2) had incomplete audiometric data (n=93); 3) were missing covariates (n=99); or 4) were missing baseline CES-D scores or reported a history of treatment for depression (n=15), leading to a final analytic sample of 2,089 participants. Analyses of the rate of longitudinal change of depressive symptoms further excluded those with fewer than two completed measures of CES-D 10 (n=1). Additionally, for the longitudinal investigation of incident depression, those with high depressive symptoms at baseline (CES-D 10 ≥ 10 at baseline; n=111) were excluded.

3.2.2 Measures

3.2.2.a Assessment of Depression and Depressive symptoms

A comprehensive assessment of depression was obtained using multiple measures. A history of self-reported treatment for depression or history of antidepressant use intended for depression was assessed at baseline. Further, the standard 20-item Center for Epidemiological Studies Depression Scale ([CES-D; years 1, 4, 6, 8, 10, and 11) or the abbreviated 10-item ([CES-D 10]; years 3 and 5) was administered to participants, allowing for up to 10 years of follow-up of depressive symptoms. Incident reported treatment for depression or reported antidepressant medication use intended for treatment of depression was collected during initial follow-up (years 2, 3, 5 and 6). To allow for maximum comparability across years of follow-up, scores on the 20-item CESD were converted to the 10-item scale as done in prior study (Irwin 1999; Andersen

1994). Scores ≥10 on the CES-D 10 have been shown to be highly sensitive in identifying participants correctly with significant depressive symptoms[19-20]. At baseline, prevalent depressive symptoms was defined as a score on the CES-D 10 of ≥ 10 or self-reported current treatment for depression. Incident depressive symptoms was defined as a change in CES-D 10 scores to a score ≥ 10 from a score of <10 or reported incident treatment for depression between years 2-11. Baseline for incident depressive symptoms was defined as year 1 (baseline) of the study.

3.2.2.b Hearing Measures

Audiometry was performed four years after baseline enrollment at Visit 5 (2001-2002). Air-conduction thresholds were obtained for each ear at 500, 1000, 2000, 4000, and 8000 Hz in a sound proof booth using an audiometer (Maico MA40) and supra-aural earphones (TDH 39). A speech-frequency pure tone average (PTA) of hearing thresholds obtained at 500-4000 Hz was calculated for the better hearing ear. Hearing loss was evaluated continuously in dB HL and categorized based on clinically defined cut points by threshold of response (no hearing loss: <25 dB HL; mild impairment: 25-40 dB HL; moderate or greater impairment > 40 dB HL). In secondary analysis, we investigated if hearing aid use attenuated the influence of hearing loss on prevalent or incident clinically significant depressive symptoms. Hearing aid use was ascertained via self-report at years 1 and 5 (binary yes/no).

3.2.2.c Other Covariates

Demographic information collected at baseline (year 1) included age, gender (categorized by sex classification assigned at birth, men vs women), race (Black vs White), education (less than high school, high school, or post-secondary education), marital status (never married, married, widowed/divorced/separated), living alone, and study site (Memphis vs Pittsburgh). Health-related factors were treated as time fixed and included history of smoking (never, former, current), cardiovascular disease history (systolic blood pressure ≥140 mm Hg, diastolic blood pressure >90 mmHg; reported history of stroke), and type 2 diabetes mellitus (use of diabetes drugs, fasting glucose ≥ 120 mg/dL) as assessed at baseline.

3.2.3 Statistical Analyses

Baseline characteristics were compared using the Wilcoxon rank-sum and Fisher's exact tests where appropriate and evaluated within each hearing category. The association between hearing and depressive symptoms was modeled both cross-sectionally and in complementary longitudinal analysis.

3.2.3.a Prevalence of depressive symptoms at baseline

We investigated differences in the prevalence of depressive symptoms and current treatment for depression by category of hearing loss at baseline using logistic regression. Models were adjusted for demographic and health factors. All analyses were further stratified by race and gender to investigate potential modification of risk. As a previous history of depressive episode is known to increase risk for future depressive episodes, in a sensitivity analysis we

also adjusted for history of depression prior to baseline as well as hearing aid use.

3.2.3.b Incident significant depressive symptoms or reported treatment for depression

The association between hearing loss and incident significant depressive symptoms was modeled using discrete time proportional hazard models among those with CES-D 10 scores <10 at baseline and not reporting current treatment for depression. The assumption of proportionality was verified using Schoenfeld residuals[21]. Year 1 was used as the time origin. Individuals had an event once they reported initiation of treatment or medication use intended for depression, or first CES-D 10 score ≥ 10. Participants were censored at the first missing observation. History of self-reported treatment for depression was adjusted for by inclusion in the baseline hazard function, as was age, education, gender, and race. In secondary analyses, models were stratified by race and gender to investigate potential modification of risk. Sensitivity analyses further adjusted for reported history of depression at baseline.

3.2.3.c Change in depressive symptoms over time

We characterized change in depressive symptoms over time using a group-based trajectory modeling approach. Trajectories of depressive symptoms were evaluated over the first 8 years of follow-up using growth mixture models (GMM), a form of trajectory modeling which models individual variation in distinct developmental paths over time as distinct classes defined by levels and trajectories of CES-D 10 scores. GMM uses a parametric finite mixture model,

and accommodates individual heterogeneity within each identified subgroup[22-24]. Mean trajectories of CES-D 10 scores were estimated in the full base analytic sample of 2,089 adults using MPlus 8.0[25] (years 1, 3, 5, 6, 8). Years of CES-D 10 were selected to include the years of richest depressive symptom data and include measures around when audiometric testing was performed. We used a maximum likelihood estimator and freely estimated within class variances. We determined the of number of trajectory classes based on recommended procedures[24], using measures of AIC, BIC, Bootstrapped likelihood ratio test, and the Lo, Mendell, Rubin likelihood ratio test. Based on these procedures (Appendix A.1), the best fitting model included 3 trajectories of depressive symptoms which was used in subsequent analyses. One class was characterized by low trajectory pattern, a second class by moderate increasing trajectory pattern, and a third class by a borderline high trajectory pattern.

To investigate if hearing loss is associated with latent class membership of depressive symptom trajectories, we used multinomial logistic regression, estimating the relative risk ratio of depressive symptom trajectory by hearing status from baseline to year 10, with normal hearing as the reference category. Models were adjusted for demographics and health factors as well as antidepressant medication use, as use of antidepressant medication may influence performance on the CES-D 10. Those who self-reported antidepressant medication use but no history of depressive symptoms or current treatment for depression were not included in the analysis. All analyses were again stratified by race and gender to investigate potential modification of risk.

Significance testing for all analyses was conducted using 2-sided tests (type I error rate=0.05). Logistic, discrete time proportional hazard, and multinomial logistic regression models were performed using STATA version 15 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3.3 RESULTS

3.3.1 Demographic and clinical characteristics

Of the 2,089 participants included in our prevalence analysis at baseline, 861 (41.2%) had normal hearing, 793 (38.0%) had a mild hearing loss, and 435 (20.8%) had a moderate or greater hearing loss, 182 (8.7%) reported a history of depression at baseline, 79 (8.3%) had clinically significant depressive symptoms or indicated current treatment for depression at baseline, and 89 (4.5%) had incident significant depressive symptoms during 10 years of follow-up. The mean CES-D 10 score at baseline was 2.9 (SD: 3.3). Demographic characteristics by hearing category are in **Table 3.1**. Those with normal hearing were more likely to be younger, women, Black participants, and have a higher education level than those with hearing loss. Participant characteristics did not differ by baseline diabetes, living alone, baseline history of hypertension, or baseline history of depression. 186 (8.9%) reported ever using a hearing aid at baseline.

3.3.2 Prevalence of depressive symptoms at baseline

Compared to normal hearing, those with a moderate or greater hearing loss experienced 2.45 times the odds (OR: 2.45, 95% CI: 1.33, 4.51) of clinically significant depressive symptoms; mild hearing loss was associated with 1.38 times greater odds (OR: 1.38, 95% CI: 0.78, 2.43) of significant depressive symptoms (**Table 3.2)**. A significant dose-response association was observed with greater odds of depressive symptoms with increasing level of hearing loss (p=0.004).

In stratified analyses, women and Black participants with hearing loss demonstrated higher odds of significant depressive symptoms compared to those with normal hearing, again demonstrating a significant dose-response association (p for trend:0.009 women, 0.013 Black); although these differences by gender and race were not statistically significant, they are remarkable for their potential public health implications. Among women, compared to participants with normal hearing, those with moderate or greater hearing loss had 2.89 times the odds of clinically meaningful depressive symptoms (OR: 2.89, 95% CI: 1.30, 6.43); those with mild hearing loss had 1.7 times greater odds (OR 1.70, 95% CI: 0.83, 3.47). Results among men were higher for those with a moderate or greater hearing loss (OR: 1.81, 95% CI: 0.69, 4.72), but not mild (mild hearing loss: OR: 0.92, 95% CI: 0.35, 2.44) compared to normal hearing. Black participants with moderate or greater hearing loss or mild hearing loss demonstrated over 3 times (OR: 3.35, 95% CI 1.25, 9.01) or over 2 times (OR: 2.24, 0.93, 5.42) greater odds of significant depressive symptoms compared to Black participants with normal

hearing, respectively. In analysis restricted to White participants, the odds of significant depressive symptoms for those with a moderate or greater hearing loss was 1.84 (OR: 1.84, 95% CI: 0.85, 3.96) with no observed difference for those with mild hearing loss (OR: 0.96, 95% CI: 1.84, 95% CI 2.06) compared to participants with normal hearing. The width of the confidence intervals in our stratified analyses prevent definitive conclusions on the associations. P-values did not support a difference in prevalence of depressive symptoms by race and gender.

Results were similar in a sensitivity analyses adjusting for reported history of treatment for depression at baseline and antidepressant use without reported treatment for depression. Secondary exploration of hearing aid use demonstrated no overall association with prevalent depressive symptoms at baseline.

3.3.3 Incidence of significant depressive symptoms by hearing status over 10 years of follow-up

Hearing loss was associated with a greater hazard for incident depression (CES-D 10 ≥ 10) for those with a moderate or greater hearing loss compared to normal hearing in the overall sample (HR: 1.26, 95% CI: 1.00, 1.58) after accounting for demographic and health factors as summarized in **Table 3.3**. We did not find significant differences in the association between hearing status and incident dementia by race or gender.

Results remained consistent after adjustment for history of treatment for depression at baseline. Self-reported hearing aid use at baseline demonstrated no association with incident depressive symptoms.

3.3.4 Change in depressive symptoms over time by hearing status

We identified three depressive symptom trajectory patterns: low, moderate increasing, and borderline high depressive symptom levels (**Figure 3.1**). Among the 2,088 participants included in the baseline analytic cohort, 1390 (66.6%) had low levels of depressive symptoms, 566 (27.1%) had moderate increasing symptoms, and 132 (6.3%) had borderline high or high symptom levels based on CESD-10 scores. The mean posterior probabilities for group membership for each trajectory are 0.967 for low, 0.832 for moderate increasing, and 0.866 for borderline high, suggesting strong classification quality.

Multinomial logistic regression results (**Table 3.4**) suggest an increased relative risk of borderline high depressive symptom trajectory compared to low depressive symptom trajectory for those with moderate or greater hearing loss compared to normal hearing. In models adjusted for demographics, health factors and antidepressant medication use, the relative risk of a borderline high depression trajectory compared to low trajectory was 1.16 (95% CI: 1.01, 1.32) for moderate or greater hearing loss compared to normal hearing and borderline significant at 1.06 (95% CI: 0.95, 1.18) for those with mild hearing loss compared to normal hearing. Results from the overall sample were marginally significant indicating the relative risk for a moderate increasing depressive symptom trajectory compared to low trajectory was 0.91 (95% CI: 0.84, 0.98) for mild hearing loss and 0.96 (95% CI: 0.87, 1.05) for moderate or greater hearing loss compared to normal hearing.

In stratified analysis, a greater relative risk of borderline high depressive symptom trajectory was noted among women and among Black participants, while a lower risk of inclusion in the moderate increasing class compared to low trajectory was observed for White participants. Effect modification by race was significant for this analysis (p=0.002). Among women with moderate or greater hearing loss a 1.25 (95% CI: 1.03, 1.52) greater relative risk of borderline high trajectory vs low trajectory was noted, compared to those with normal hearing, but no significant differences were observed for mild loss compared to normal hearing. Among Black participants, a relative risk of a borderline high depressive symptom trajectory was 1.24 (1.24, 95%CI: 1.04, 1.48 moderate loss) and 1.58 (1.58, 95%CI: 1.24, 2.03 mild loss) compared to low trajectory. A lower relative risk was observed for a moderate increasing trajectory compared to the low trajectory class among White participants with any hearing loss compared to normal hearing, but no difference was noted for borderline high trajectory compared to low for either category of hearing loss among White participants. As before, the width of the confidence intervals in our stratified analysis limits conclusions in the associations by gender. P-values suggested a difference in the association of trajectory class by race (p=0.002 borderline high trajectory; p=0.001 moderate increasing trajectory).

3.4 DISCUSSION

In this demographically diverse population-based cohort of 2,089 older adults in the United States with up to 10 years of follow-up, we investigated the

impact of hearing loss on depressive symptoms using a comprehensive definition of depression which incorporates self-reported history of depression, medication use, and questionnaires. Those with hearing loss demonstrated significantly greater odds of clinically significant depressive symptoms at baseline and suggest greater risk for incident clinically significant depressive symptoms over follow-up. Results were robust even after covariate adjustment and consideration of a history of treatment for depression. Analysis of depressive symptoms over time suggest greater risk for a poorer depressive symptom trajectory for those with hearing loss, particularly moderate or greater loss, compared to those with normal hearing. Estimates were higher among women and among Black participants in both baseline prevalence and investigation of change in depressive symptoms over time.

Our results are consistent with the preceding work by Brewster et al[11] which demonstrated a cross-sectional association between low and mid-frequency hearing status and depressive symptoms on CES-D 10 scores at year 5 of the Health ABC study. Moreover, that work suggested 1.63 times the odds of an increasing depressive symptom trajectory and 1.85 times the odds of a consistently high depressive symptom trajectory for those reporting any age-related hearing loss compared to those reporting no hearing loss. This prior work uniquely accounted for the complex nature of late-life depression by capitalizing on the longitudinal depression measures in HABC and incorporating a measure of depressive symptom trajectory over time. With expansion on this prior work, we reached similar findings, using a multi-faceted characterization of depression

in addition to conducting stratified analyses to investigate potential differences in these associations by race and gender. Cacciatore et al[26], suggested a positive relationship (r=0.85) between older adults with hearing difficulty and depressive symptom scores. A meta-analysis[27] including studies of chronic diseases and risk for depression in old age reported a pooled odds ratio of 1.71 for the odds of prevalent depression among those with poor hearing (not defined by the authors) and a pooled relative risk of 1.92 for incident depression among those with poor hearing compared to normal. An additional study from the Health ABC cohort by Contrera et al[28] observed that compared to those with normal hearing, older adults with moderate or greater hearing loss demonstrated a 28% decreased odds of emotional vitality defined as a high sense of personal mastery, and high levels of happiness, and lower levels of depressive symptoms or anxiety.

While consistent with these previous findings, our analysis undertook a more comprehensive approach to characterize the association in both cross-sectional and longitudinal models using an established and validated questionnaire for depression. We observe significant associations between hearing loss and depressive symptomatology at baseline. The severity of depressive symptoms at the start of follow-up seemed to make a large contribution towards symptomatology measured. Even our classification of depressive symptom trajectory was dependent upon the degree of depressive symptoms at baseline, even after adjustment for history of depression. Longer follow-up for depressive symptoms starting in late mid-life may shed light on

sensitive periods for development of depression among hearing impaired older adults.

Differences in the relationship between hearing impairment and depressive symptomatology by race and gender may potentially highlight the interconnected relationship between influences of social structure, communication ability, and depressive symptomatology for older adults. Prior evidence has suggested differences in late-life depression by gender and race[17,29-31] yet few, if any, prior studies have attempted to quantify the association between hearing loss and depression by gender or race. While our analyses do not support an interaction between hearing loss and race or hearing loss and gender, we did observe differences in the magnitude of associations. A higher association between hearing loss and prevalent depressive symptoms, and overall poorer depressive symptom trajectory was observed among Black participants with a moderate or greater hearing loss vs normal over 10 years of follow-up than estimates observed among Whites. Similarly, a poorer depressive symptom trajectory was observed among women with a moderate or greater hearing loss. In contrast, among White participants with hearing loss compared to those with normal hearing, a lower risk of being in the moderate increasing trajectory compared to the low depressive symptom trajectory was observed, even after accounting for other demographic factors.

Our use of several methods to represent the phenomenology of depression helps to better encapsulate the complex presentation of depression in older adults. While depression is overall less prevalent in older adults compared

to younger adults[32], it is possible even one episode of depression is associated with significant negative outcomes (i.e., dementia, increased mortality, slower medical recoveries, increased disability)[32-33]. Late-life depression often has a differing presentation than depression at younger ages which warrants greater understanding for potential intervention[34]. Older adults are more likely than younger adults to endorse loss of interest in life or activities or express somatic symptoms[32]. While much remains in the identification of risk factors for late-life depression in older adults, a complex relationship between biological changes and vulnerabilities, stressful events, curtailment of daily activities, and self-criticism may predispose an older adult to depressive symptoms[5, 31-32]. Hearing loss may therefore increase risk for late-life depression as a result of withdrawing from social activities and reduced engagement from difficulty communicating. Hearing impaired older adults may also become discouraged by their inability to have quality connections with others leading to downstream psychosocial effects like social isolation, loneliness, and depression. A biological basis with brain changes associated with hearing loss has been hypothesized as a mechanism for the association and warrants further study[5]. Even with the modest increased risk demonstrated in our analysis, consideration of hearing loss as a risk factor for depression is notable owing to the high prevalence of hearing loss and its potential treatability with hearing aids. Further characterization of how the intersectionality of race and gender (i.e., Black women, White women, Black men, and White men) among hearing impaired older adults may influence depressive symptoms presents opportunity for innovation in how each group may

cope with hearing loss given life and social circumstances. Additionally, management of hearing loss has the potential to improve existing intervention strategies for late-life depression. The ability to maintain quality communication with managing physicians and adequately engage in intervention strategies like cognitive behavioral therapy or interpersonal therapy for late-life depression deserves further study but has the potential to supplement current management strategies. Reducing the clinical and social burden of late-life depression through aural rehabilitation and combined existing depression intervention strategies could have far-reaching incidental benefit.

Prior research on the effect of race and gender on late-life depression has indicated increased risk among women compared to men and among Black individuals compared to non-Hispanic White individuals. When investigating racial differences, a cross-sectional study of over 50,000 older adults[30] indicated significantly greater odds of anhedonia (i.e., inability to feel pleasure), psychomotor symptoms and sadness among Black participants compared to non-Hispanic White participants. Results were robust even after adjustment for social and health determinants such as socioeconomic status, lifestyle factors (i.e., body mass index, physical activity, smoking and alcohol use), or comorbidities. Moreover, it is possible hearing loss increases vulnerability to the social and emotional strain and inequalities faced by many minority individuals in the U.S.[17]. This vulnerability might therefore predispose minority individuals to increased depressive symptoms. Further, it is possible the prolonged communication strain from significant hearing loss may add to strain from known

societal inequalities and racial disparities, leading to the higher relative risk or poorer depressive symptom trajectories observed in our analysis over time for Black participants. Known disparities in access to health care, utilization of health services, and delays to the initiation of psychosocial treatment between Black and White individuals exist[30], which may potentially exacerbate this vulnerability. Further characterization of how hearing loss may have differing social and emotional effects by race may highlight potential avenues for intervention of depression.

Prior results also suggest greater odds of depressive symptoms including depressed mood and somatic complaints among older women compared to older men (Abrams 2019). Our findings are consistent with this prior work, and remained consistent across measures of hearing difficulty. Prior hypotheses have suggested social factors may lead older women to place greater emphasis then older men on spoken communication to maintain connection with others[5-6]. Therefore, due to these social influences, hearing loss may have a greater impact on this feeling of connection in women and may result in the higher baseline prevalence and greater dose response over time observed in our study. Future investigation of the inter-relational effect of race and gender among hearing impaired older adults may aid in determining particular groups at the greatest risk of depressive symptoms as well as provide opportunity for personalized intervention for late-life depression.

While the longitudinal nature of our study is a strength, we acknowledge the limitation of audiologic measures completed 4 years after baseline. We

elected to use the full 10 years of rich depression measures available by using Year 1 as baseline for our analysis. While this presents a chronological gap from when hearing was measured, for the majority of older adults, hearing changes very gradually at a rate of 1-2 dB per year[35] and is an approach which has been used in other studies[36-37]. Therefore, the time between baseline and when audiometry was performed likely only presents a minimal change in hearing for most participants. We therefore do not expect significant misclassification by hearing category – any misclassification would likely lead to a conservative estimate of the association observed between hearing and depressive symptoms across the analyses performed. We were additionally not able to assess medication use for depression beyond year 6. Albeit the CES-D 10 demonstrates good sensitivity in identifying those with significant depressive symptoms, it is not a diagnostic measure for depression. It is possible this assessment may incorrectly capture constructs of depression which are more appropriate for older adults and result in misclassification of depressive symptoms. Additionally, it is possible we may underestimate depressive symptomatology among older adults or subgroups from participants' hesitation to report depressive symptoms or seek treatment due to stigma associated with depression. However, a strength of our analysis is the multiple modes by which we are able to assess depressive symptoms in our study population which may better capture the presence of symptomatology. Cross-sectional measures of depression may be subject to episodic depressive symptoms related to situational circumstances such as stressful life events (i.e., death of a spouse, significant medical diagnosis) and

therefore may not correctly reflect longer term levels of depression. Our study includes both cross-sectional measures, for comparability to previous studies, as well as two different means to assess longitudinal depression over time. This comprehensive assessment may more accurately reflect depressive symptomatology in older adults through utilization of depression questionnaires, self-report history for treatment or diagnosis, and use of medications prescribed for depression.

Our results investigating reduced risk of depression among hearing aid users yielded findings which were not statistically significant. However, our measure of hearing aid use included self-report hearing status. Individuals commonly over-estimate their use of a hearing aid[38] and may therefore lead to misclassification of hearing aid use in our participants and contribute to our null findings. The potential benefit of hearing aid use for management of hearing loss and reducing depression risk is substantial. Therefore, future study with more sophisticated evaluation of hearing aid use and appropriate device fitting could have far reaching clinical and public health benefit.

In a longitudinal cohort study of older adults, results support an association between greater degree of hearing loss and both prevalent and incident clinically significant depressive symptoms, particularly for those with a moderate or greater hearing loss. We observed suggestion of an association between hearing loss and a borderline high clinically significant depressive symptom trajectory over 10 years of follow-up. Higher associations were observed among women and Black participants, warranting further study. Clinical

providers working with older adults might consider the patient's hearing status when addressing risk factors for late-life depression, as well as disparities in psychosocial care by race and gender. As hearing loss is modifiable with the use of hearing intervention strategies, understanding how hearing loss may increase risk for depressive symptoms, especially in subgroups of older adults, and if hearing aids have the potential to be considered an intervention option for late-life depression could significantly improve psychosocial outcomes for older adults.

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Table 3.1 Baseline Demographics of the Analytic Sample and by Hearing Status in HABC (N=2,089)

	Overall (N= 2,089)	Normal hearing (N=861)	Mild hearing loss (N=793)	Moderate or greater hearing loss (N=435)	p-value*
	N (%)	N (%)	N (%)	N (%)	
Baseline Age, mean (SD)	74.0 (2.8)	73.3 (2.7)	74.2 (2.8)	74.8 (2.9)	<0.001
PTA, mean (SD)	30.3 (13.5)	18.2 (5.1)	32.6 (4.3)	50.4 (9.1)	<0.001
Black	793 (38.0)	406 (47.2)	275 (34.7)	112 (25.7)	<0.001
Women	1082 (51.8)	531 (61.7)	398 (50.2)	153 (35.2)	<0.001
Education					0.033
Postsecondary	933 (44.7)	391 (45.4)	364 (45.9)	178 (40.9)	
High School grad	693 (33.2)	288 (33.4)	269 (33.9)	136 (31.3)	
Less than High School	463 (22.2)	182 (21.1)	160 (20.2)	121 (27.8)	
Memphis study center	1023 (49.0)	392 (45.5)	395 (49.8)	236 (54.3)	0.010
Marital Status					0.012
Never Married	102 (4.9)	41 (4.8)	40 (5.0)	21 (4.8)	
Married	1219 (58.4)	466 (54.1)	479 (60.4)	274 (63.0)	
Widowed, Divorced, Separated	768 (36.8)	354 (41.1)	274 (34.6)	140 (32.2)	
Live Alone	603 (28.9)	268 (31.1)	218 (27.5)	117 (26.9)	0.16
Baseline Diabetes	727 (34.8)	279 (32.4)	282 (35.6)	166 (38.2)	0.10
BMI, mean (SD)	27.4 (4.7)	27.4 (4.9)	27.4 (4.8)	27.1 (4.1)	0.48
Smoking History					<0.001
Never smoker	950 (45.5)	434 (50.4)	355 (44.8)	161 (37.0)	
Former smoker	969 (46.4)	353 (41.0)	384 (48.4)	232 (53.3)	
Current smoker	170 (8.1)	74 (8.6)	54 (6.8)	42 (9.7)	
Baseline history of CVD	1379 (66.0)	575 (66.8)	523 (66.0)	281 (64.6)	0.73
Baseline history of depression	182 (8.7)	69 (8.0)	68 (8.6)	45 (10.3)	0.37
CES-D 10 score, mean (SD)	2.9 (3.3)	2.8 (3.1)	2.8 (3.4)	3.0 (3.4)	0.52

*Baseline characteristics were compared using Wilcoxon rank-sum tests and Fisher's exact tests

Notes: PTA= pure tone average; SD= standard deviation; BMI= body mass index; CVD= cardiovascular disease; CES-D 10= Center for Epidemiologic Studies Depression scale short form; Mild hearing loss= PTA 25-40 dB HL; moderate or greater hearing loss= PTA>40 dB HL

Table 3.2 Cross-sectional prevalence of clinically significant depressive symptoms or treatment for depression at baseline (1997-1998) by hearing category, race, and sex in HABC (N=2,089)

	Normal hearing Odds Ratio [95% CI]	Mild Hearing Loss Odds Ratio [95% CI]	Moderate or greater Hearing Loss Odds Ratio [95% CI]	P for trend*
Overall (N=2,089)	1.0 (Reference)	1.38 [0.78,2.43]	**2.45 [1.33,4.51]**	0.004
Women (N=1,082)	1.0 (Reference)	1.70 [0.83,3.47]	**2.89 [1.30,6.43]**	0.009
Men (N=1,007)	1.0 (Reference)	0.92 [0.35,2.44]	1.81 [0.69,4.72]	0.190
Black (N=793)	1.0 (Reference)	2.24 [0.93,5.42]	**3.35 [1.25,9.01]**	0.013
White (N=1,296)	1.0 (Reference)	0.96 [0.45,2.06]	1.84 [0.85,3.96]	0.126

Models adjusted for demographic (age, gender, race, education) and health factors (study site, marital status, living alone, diabetes, Body mass index, cardiovascular disease history)
Notes: Normal hearing defined as PTA<25 dB HL, Mild hearing loss PTA >25 dB HL and ≤ 40 dB HL; Moderate or greater hearing loss as PTA >40 dB HL

Table 3.3 Incidence of new clinically significant depressive symptoms or incident treatment for depression over 10 years (1997/1998 to 2007/2008) by hearing category, race, and sex in HABC (N= 1,978)

	Normal hearing	Mild Hearing Loss	Moderate or greater Hearing Loss	P for trend*
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Overall (1,978)[a]	1.0 (Reference)	1.15 [0.96,1.39]	**1.26 [1.00,1.58]**	0.037
Women (1,014)[b]	1.0 (Reference)	1.15 [0.91,1.46]	1.33 [0.97,1.83]	0.062
Men (964)[b]	1.0 (Reference)	1.16 [0.86,1.55]	1.20 [0.86,1.66]	0.273
Black (744)[b]	1.0 (Reference)	1.11 [0.85,1.45]	1.22 [0.86,1.74]	0.239
White (1,234)[b]	1.0 (Reference)	1.20 [0.90,1.48]	1.26 [0.94,1.68]	0.066

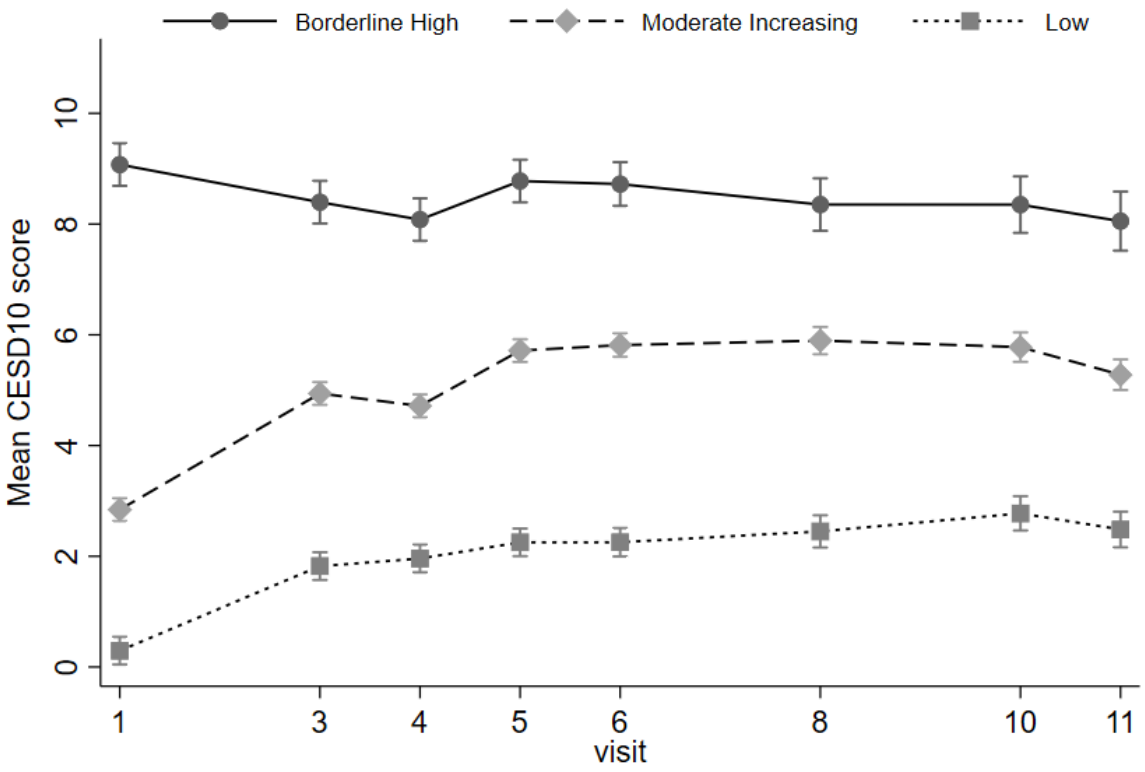
[a]Overall model fully adjusted for demographics (age, gender, race, education) and health factors (study site, marital status, living alone, diabetes, Body mass index, cardiovascular disease history)

[b] stratified models adjusted for demographics (age, gender/race, education) and excluding those reporting antidepressant use but not treatment for depression

Notes: Normal hearing defined as PTA<25 dB HL, Mild hearing loss PTA >25 dB HL and ≤ 40 dB HL; Moderate or greater hearing loss as PTA >40 dB HL

*α=0.05

Figure 3.1 Mean CES-D 10 score per Depressive Symptom Trajectory across 10 years of follow-up (1997/1998 to 2007/2008) in HABC Study



Notes: Depressive symptom trajectory created using Center for Epidemiologic Study Depression scale short-form (CES-D 10) responses from visits 1, 3, 5, 6, and 8
27.1% of participants were in the moderate increasing trajectory; 66.6% in the low depressive symptom trajectory; 6.3% in the borderline high depressive symptom trajectory

Table 3.4 Relative risk ratio of depressive symptom trajectory over 10 years (1997/1998 to 2007/2008) by hearing category, race, and sex in HABC (N= 2,088)

	Overall	Women	Men	Black	White
Borderline high trajectory (N=132)					
Mild hearing loss	1.06 [0.95,1.18]	1.10 [0.95,1.26]	1.03 [0.86,1.23]	**1.24 [1.04,1.48]**	0.95 [0.82,1.09]
≥Moderate hearing loss	**1.16 [1.01,1.32]**	**1.25 [1.03,1.52]**	1.09 [0.89,1.32]	**1.58 [1.24,2.03]**	1.05 [0.89,1.24]
Moderate Increasing trajectory (N=566)					
Mild hearing loss	**0.91 [0.84,0.98]**	0.93 [0.84,1.03]	0.89 [0.80,1.00]	1.07 [0.94,1.21]	**0.83 [0.75,0.91]**
≥Moderate hearing loss	0.96 [0.87,1.05]	1.01 [0.86,1.17]	0.94 [0.83,1.07]	**1.43 [1.19,1.73]**	**0.83 [0.74,0.93]**
Low trajectory (N=1,390)					
Mild hearing loss	Reference -	Reference -	Reference -	Reference -	Reference -
≥Moderate hearing loss	Reference -	Reference -	Reference -	Reference -	Reference -

Notes: Depressive symptom trajectory created using Center for Epidemiologic Study Depression scale short-form (CES-D 10) responses from visits 1, 3, 5, 6, and 8
Models adjusted for demographics (age, gender, race, education) and health factors (study site, marital status, living alone, diabetes, Body mass index, cardiovascular disease history, antidepressant medication use)
27.1% of participants were in the moderate increasing trajectory; 66.6% in the low depressive symptom trajectory; 6.3% in the borderline high depressive symptom trajectory
Normal hearing defined as PTA<25 dB HL, Mild hearing loss PTA >25 dB HL and ≤ 40 dB HL; Moderate or greater hearing loss as PTA >40 dB HL

CHAPTER 4: Examining the Combined Estimated Effects of Hearing Impairment and Depressive Symptoms on Risk of Cognitive Decline and Incident Dementia in the Health ABC Study

ABSTRACT

Objective: The combination of two highly prevalent risk factors for dementia – hearing loss and depressive symptoms – may present unique risk of dementia for older adults. We aimed to test if rates of cognitive decline or incident dementia differ for participants with both hearing loss and depressive symptoms compared to what would be expected given their independent effects.

Methods: Data were from the Health, Aging, and Body Composition Study (Health ABC), a longitudinal study of well-functioning community-dwelling older adults. Rates of 8-year cognitive change on the Modified Mini Mental State Exam and Digit Symbol Substitution Test were evaluated, and incident dementia was defined using a predetermined algorithm incorporating medication use, hospital records and neurocognitive tests. Depressive symptomatology was defined in 3 ways, CES-D 10 ≥ 10: (i) Baseline: on the exam at baseline; (ii) Persistent: at both of the first 2 times points; or (iii) Repeated: more than one year during the first 4 years of follow-up (not required to be consecutive). Hearing loss was determined via pure-tone average (PTA) in the better hearing ear at 500-4000 Hz and categorized as normal or mild hearing loss (PTA<40 dB HL) vs moderate or greater hearing loss hearing loss (PTA ≥ 40 dB HL). Associations between hearing loss, depressive symptoms and rates of cognitive decline or incident dementia were assessed using linear mixed effects models and Cox proportional hazards models, respectively.

Results: The coupling of hearing loss and depressive symptoms – regardless of how either was defined – is associated with faster rates of cognitive decline

compared to the group with no significant hearing loss or depressive symptoms. The hazard for incident dementia was greatest among the group with both moderate or greater hearing loss and either baseline depressive symptoms (HR: 3.81, 95% CI: 1.90, 7.62) or repeated depressive symptoms (HR: 2.91, 95% CI: 1.59, 5.33).

Conclusion: The combined presence of both hearing loss and depressive symptomatology (particularly symptoms lasting for more than one year) presented the fastest rates of cognitive change on cognitive tests as well as greatest risk for incident dementia, compared to those with no significant hearing loss or depressive symptoms. The observed estimated effect was greater than the independent estimated effect of each risk factor. Subgroups of older adults with hearing loss who further present with depressive symptomatology may introduce a unique opportunity for clinical and public health intervention for prevention of dementia.

4.1 INTRODUCTION

With the growing prevalence of dementia in the United States, there is a pressing need to identify potential avenues for prevention of dementia and cognitive decline. In the U.S., an estimated 5.8 million individuals were living with Alzheimer's disease in 2020, expected to increase to nearly 14 million by 2050[1]. Hearing impairment is an independent and modifiable risk factor for dementia[2]. Over two-thirds of adults over the age of 70 years have a hearing loss[3]. Moreover, around 67% of older adults of Medicare age have multimorbidity[4]; therefore, hearing impairment is likely present in older adults along with other health conditions. Given the high prevalence of hearing impairment in older adults, identification of differences in dementia risk by subgroups of older adults with concurrent modifiable risk factors for cognitive decline could have meaningful public health benefit.

Late-life depression is one such potential comorbidity that may co-occur in older adults with hearing loss, as the prevalence of depressive symptoms is estimated at around 15% in a community-sample of older adults[5]. Depressive symptomatology in older adults may present as a heterogeneous course, susceptible to variation over time or acute instances from life events[5]. Furthermore, depression itself has been identified as another independent modifiable risk factor for dementia[2].

While the independent effects of hearing impairment, clinical depression and increased depressive symptoms on cognitive decline and dementia in older adults have been reported[2,6-7], the estimated effect from the presence of both

conditions has received little study. A prior study of 8,529 participants aged 60 years or older from the National Alzheimer's Coordinating Center Uniform Data Set, one of the few studies to consider both hearing loss and depression, investigated the potential mediating effect of depression and found no evidence of suggested change in the hearing loss-dementia association[8]. Although mediation analyses have benefit for understanding mechanisms, analyses of modification (i.e., interaction) have important public health relevance for the identification of high-risk groups. As hearing loss and depression are both potentially modifiable, understanding if the risk presented by each condition in isolation differs from the risk in the presence of both conditions may allow for more targeted dementia intervention efforts in older adults.

Our study objectives, using data from the Health Aging and Body Composition (Health ABC) study, are to test if (i) rates of cognitive decline and (ii) risk of incident dementia differ for participants with both hearing loss and depressive symptoms compared to what would be expected given their independent effects. We hypothesized the additional presence of depressive symptomatology among hearing impaired older adults demonstrates faster rates of cognitive decline and greater risk of incident dementia.

4.2 METHODS

4.2.1 Study Population

Participants were enrolled in the Health ABC study, a biracial prospective study of 3,075 community dwelling older adults, aged 70-79 years at study initiation in 1997-1998 (visit 1), recruited from Pittsburgh, Pennsylvania or Memphis, Tennessee[9]. As the Health ABC Study was designed to assess differences in function, disability, and longevity across race (Black vs. White) and gender, participants enrolled in the study were free of difficulty walking ¼ mile or difficulty climbing up 10 steps at baseline. This study was approved by the Institutional Review Boards of all participating institutions. Audiometric hearing was assessed at study year 5 (2001-2002).

4.2.1.a Analytic Sample: Rates of Cognitive Decline

From an initial sample of 3,075, a total of 2,198 participants had complete audiologic measures (872 excluded), and completed the baseline Center for Epidemiologic Study depression scale (CES-D) and self-reported depression medication use measured at baseline (5 excluded). We excluded 137 participants who were missing baseline covariates or had less than 2 measures of the Modified Mini-Mental State Exam (3MS) or the Digit Symbol Substitution Test (DSST) during the 10 years of follow-up. Our final analytic sample was 2,061.

4.2.1.b Analytic Sample: Incident Dementia

Of the 2,034 study participants who had complete audiologic measures in 2001-2002 (872 excluded), were dementia free at visit 1 (1997-1998) (159

excluded), and had completed baseline CES-D scores (10 excluded), an additional 214 participants were missing covariate data leading to an analytic sample in our secondary analysis of 1,820 participants.

4.2.2 Cognitive Decline

Two neurocognitive tests, the Modified Mini-Mental State Exam (3MS)[10] and the Digit Symbol Substitution Test (DSST)[11] were collected six times during the study: Year 1 (1997-1998), Year 3(1999-2000), Year 5 (2001-2002), Year 8 (2004-2005), Year 10 (2006-2007) and Year 11 (2007-2008).

As a test of global cognitive function, the 3MS[10] provides an assessment of an individual's orientation, registration, attention, calculation, recall and visual-spatial skills similar to the 30-item Mini-Mental State exam (MMSE)[12] it was adapted from. Expanded from the 30-item MMSE and scored from 0-100, this modification from the 30-item scale is designed for enhanced reliability and validity.

The DSST[11] tests attention, processing speed, and executive function requiring the participant to use a key of symbols and matched numbers to translate the corresponding number and symbol as fast as possible. Scoring is completed as the total number of symbols correctly matched within 90 seconds time - higher scores indicate better performance.

4.2.3 Incident Dementia

As has been implemented in prior work[13-14], incident dementia was defined as initiating use of a prescribed dementia medication (galantamine, rivastigmine,

memantine, donepezil, or tacrine), a dementia diagnosis from adjudicated hospital records, or a race-stratified 3MS decline of more than 1.5 standard deviations from the baseline mean. Medication use and hospital records were assessed annually.

4.2.4 Hearing Loss

Hearing acuity measures were performed via audiometry in a sound-proof booth at Year 5 (2001-2002). Air conduction thresholds, as measured in decibels hearing level (dB HL), were completed in each ear from 250 Hz to 8000 Hz with TDH 39 headphones using a MA40 audiometer (Maico Diagnostics, Eden Prairie, MN) calibrated to the American National Standards Institute standards (ANSI S3.6-1996).

For comparison of hearing levels, we calculated a commonly used metric of the speech frequency pure tone average (PTA) using thresholds at 500, 1000, 2000, and 4000 Hz in the better hearing ear in agreement with the World Health Organization's definition of hearing loss[15]. We created a binary variable of hearing loss according to common clinical cutpoints (normal hearing or mild hearing loss, PTA<40 dB HL; moderate or greater hearing loss, ≥40 dB HL). Moderate or greater hearing loss is recognized as a level at which hearing impairment begins to adversely affect communication ability[16].

4.2.5 Depressive Symptoms

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)[17], including both the full 20-item scale (Year 1) and abbreviated 10-item scale (Years 3-11). All scores were converted to the CES-D 10 scale. For our analysis, we utilized CES-D 10 scores from the start of follow-up until when hearing was assessed (Years 1, 3, 4, and 5) and defined significant depressive symptoms as a CES-D 10 score ≥10[18-19]. A history of having ever been treated for depression was ascertained at Year 1. Baseline depressive symptoms were therefore defined as a CES-D 10 score ≥10 at Year 1 or the presence of medication intended for depression. In order to better understand how the potential variability in depressive symptom presentation over time might modify the hearing-dementia relationship, we modeled depressive symptoms incorporating repeated measures in two ways. First, we modeled persistent depressive symptoms, defined as elevated CES-D 10 scores (≥10) at both Years 1 and 3 or reported treatment for depression, with the goal of capturing ongoing depressive symptomology rather than acute instances that may be related to transient life events. Second, we modeled repeated depressive symptoms as any repeated instance (consecutive or not) of clinically significant depressive symptoms (≥1 elevated CES-D 10 score at Years 1, 3, 4 or 5) (**Table 4.1**).

4.2.6 Additional Independent Variables

We included age (years), gender (determined from sex identified at birth; women/men), race (Black/White), study center (Memphis or Pittsburgh) and

education (less than post-secondary vs post-secondary or greater) as measured at Year 1 (1997-1998). We also included a number of health related factors. Diabetes was considered present if prevalent at Year 1, defined as physician-diagnosed diabetes (reported by the participant), use of diabetes drug, or a fasting glucose ≥126mg/dL. Hypertension was considered present if prevalent at baseline (systolic blood pressure ≥140 mmHg, or diastolic blood pressure >90 mmHg, or by participant self-report of a diagnosis by a physician with or without antihypertensive medication use). History of stroke was assessed at baseline by the question, “Has a doctor ever told you that you had a stroke, mini-stroke, or TIA?”. Smoking status (ever vs. never) was assessed at baseline by the questions “Do you smoke cigarettes now” and “Have you smoked at least 100 cigarettes in your life”. Body mass index (BMI, continuous kg/m) was evaluated at baseline. Marital status (never married, married, widowed/divorced/separated) was evaluated with the question “What is your marital status”. Living alone (yes/no) was defined as reported presence of living with one or more individuals vs none. As it is possible hearing aid use for the management of hearing loss may influence the estimated risk presented by hearing loss alone or in the presence of other conditions, in a sensitivity analysis, we will additionally adjust for self-reported hearing aid use at baseline. All time-varying covariates were measured at baseline, except for hearing aid use, which was measured at Year 5.

4.2.7 Statistical Analysis

Descriptive analysis compared demographic information and clinical characteristics across level of hearing status. Baseline characteristics were compared using means and standard deviations and ANOVA tests for continuous measures. Categorical variables were described using frequencies with differences tested using chi-square tests.

We used linear mixed effects models with person-specific slopes and intercepts to assess differences in rates of cognitive decline by hearing and depressive symptom status. Cognitive decline on the DSST and 3MS was modeled separately. The linear mixed model accounts for the correlation between repeated measures over time within an individual[20]. We assumed an unstructured correlation matrix. We used Cox proportional hazard models to investigate risk of incident dementia by depressive symptom status and category of hearing acuity over 9 years of follow-up. We confirmed the proportionality assumption via Schoenfields residuals[21] and included an interaction between our exposure and time. For assessment of incident dementia, time on study was used as the time scale, with Year 3 (1999-2000) as the time origin. As most participants were not at risk for incident dementia until the second administration of the 3MS at Year 3, our time origin was modeled as Year 3 (1999-2000). For our analysis, follow-up for incident dementia continued until Year 11 (2007-2008) at the last time the 3MS was administered to our study sample

We described differences in the association of hearing and cognition by depressive symptom status in two ways, as has been recommended for

observational studies[22-23]: (1) modelling the joint risk of dementia using 4 exposure categories – (i) normal hearing or mild hearing loss and no depressive symptoms (reference group), (ii) depressive symptoms only, (iii) hearing impairment only, and (iv) both hearing impairment and depressive symptoms and (2) inclusion of an interaction term between hearing impairment and depressive symptoms in the regression model. In our analysis of incident dementia, we also stratified results of the hazard of incident dementia from hearing loss by depressive symptoms status, as well as the hazard from depressive symptoms by hearing status. This framework enabled us to assess the presence of both joint effects (i.e., 4 exposure categories) and heterogeneity of effects (i.e., interaction term) of depressive symptoms and hearing loss on cognitive outcomes.

Model fit for both analyses was assessed using residual plots and through statistical methods including the Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and likelihood ratio tests. As the additive scale has important public health implications[24], for our analysis of incident dementia we present the independent and combined estimated effect of exposures on the additive scale using the relative excess risk of interaction (RERI) and the synergy index (ratio between the combined effect of an exposure and the individual effects)[25-26] and include a 95% confidence interval calculated via the delta method[22, 27].

We adjusted for gender, education (post-secondary vs less than post-secondary), age, race (Black vs White), smoking (ever vs never), the presence or

absence of hypertension or diabetes, body mass index (BMI), marital status (never married, married, widowed/divorced/separated), and living alone. All analysis were completed using STATA 15.0 (StataCorp. 2017).

4.2.7.a Sensitivity Analysis

In a sensitivity analysis, we additionally adjusted for self-reported hearing aid use at baseline to understand if management of hearing loss may alter the effect estimates observed. Additionally, we repeated our analysis evaluating the combined estimated effects of hearing loss and depressive symptoms on cognitive decline and incident dementia using Year 5 as the study baseline, as that is when hearing was measured.

4.3 RESULTS

4.3.1 Descriptive Analysis

In our analytic sample of 2,061 participants, 20.7% had a moderate or greater hearing loss, and 7.1% had clinically significant depressive symptoms at baseline. Sixty-one participants (3.0%) experienced persistent depressive symptoms at both Years 1 and 3, while 220 (10.7%) had repeated depressive symptoms over the first 4 years of follow-up. Categorizing participants based both on hearing status and baseline depressive symptoms, 1,529 (74.2%) had normal hearing or mild hearing loss and no baseline depressive symptoms, 385 (18.7%) had a moderate or greater hearing loss only, 104 (5.0%) had clinically significant depressive symptoms at baseline only, and 43 (2.1%) had both

significant hearing loss and depressive symptoms. Those without significant hearing loss or depressive symptoms were generally younger and female compared to those with hearing loss and/or depressive symptoms (**Table 4.2**).

4.3.2 Baseline Cognitive Test Performance and Rates of Cognitive Decline

Compared to participants with neither significant hearing loss nor baseline depressive symptoms, participants with a moderate or greater hearing loss (without depressive symptoms) on average had lower baseline test scores (-0.86; 95% CI: -1.53, -0.18 on 3MS; -0.81; 95% CI: -2.08, 0.47 on DSST), and faster rates of decline on both the 3MS (-0.14; 95% CI: -0.26, -0.02) and DSST (-0.17; 95% CI: -0.29, -0.05). Results were consistent across all ways of measuring depressive symptoms (**Table 4.3**).

The association between depressive symptoms alone, without hearing impairment, varied by how depressive symptoms were measured. We found no evidence of an association between baseline depressive symptoms and baseline test performance or rates of cognitive decline. Persistent depressive symptoms (depressive symptoms reported at Year 1 and Year 3) was associated with lower baseline DSST scores (-3.25; 95% CI: -6.20, -0.30) but not with baseline 3MS scores, nor with rates of decline in either test. However, depressive symptoms at repeated visits (depressive symptoms at more than one time point between Year 1 and Year 5) was consistently associated with poorer baseline scores (-1.34; 95% CI: -2.30, -0.38 on 3MS; -1.94; 95% CI: -3.77, -0.11 on DSST) and faster rates of cognitive decline for both tests (-0.21; 95% CI: -0.37, -0.05 on 3MS; -0.21; 95% CI: -0.40, -0.03 on DSST) (**Figure 4.1)**.

When considering the estimated joint effect for both hearing loss and depressive symptoms, moderate or greater hearing loss and persistent depressive symptoms, compared to no hearing loss or mild loss and no depressive symptoms, was associated with lower average baseline test scores on the 3MS (-1.91; 95% CI: -3.74, -0.09). We found no associations for hearing loss plus other measures of depressive symptoms (baseline, repeated) on baseline 3MS scores, or on the DSST at baseline. However, faster rates of cognitive decline were observed across all measures and tests, significantly faster with repeated depressive symptoms on the DSST (-0.64; 95% CI: -1.27, -0.01) and on both tests for persistent depressive symptoms (-0.30; 95% CI: -0.78, -0.19 3MS; -0.35; 95% CI: -0.67, -0.03).

4.3.3 Incident Dementia

Over 9 years, 223 (12.2%) participants developed incident dementia. Relative to those without significant hearing loss (normal hearing or mild hearing loss) or clinically meaningful depressive symptoms, those with moderate or greater hearing loss demonstrated a significantly greater risk of incident dementia across all ways of measuring depressive symptoms (HR: 1.42, 95% CI: 1.03, 1.95 baseline symptoms and 1.54, 95% CI: 1.10, 2.15 repeated symptoms) (**Table 4.4**).

The association in those with clinically significant depressive symptomatology alone without hearing impairment is suggestive of greater risk for baseline depressive symptoms (HR: 1.70, 95% CI: 0.92, 3.15) and indicates

greater risk for incident dementia with repeated depressive symptoms over the first 4 years of follow-up (HR: 2.35, 95% CI: 1.56, 3.53) (**Figure 2)**.

The strongest estimated risk for incident dementia was observed for the presence of both hearing loss and depressive symptoms across both measures of depressive symptoms used (HR: 3.81; 95% CI: 1.90, 7.62 baseline; HR: 2.91; 95% CI: 1.59, 5.33 repeated).

To present results on an additive scale, the relative excess of interaction (RERI) for baseline depressive symptoms is suggestive of an interaction (RERI: 1.69. 95% CI: -1.10, 4.47), though not significant. A measure of the excess risk from exposure to both exposures relative to the risk from no exposure interaction[27] (Synergy Index) again suggests a departure from additivity (S: 2.51; 95% CI: -0.87, 5.88) for baseline depressive symptoms. Our investigation of the heterogeneity of the effects of each exposure on incident dementia, while not statistically significant, suggests heterogeneity in the degree of risk, with greater risk presented by the presence of both comorbid conditions (**Figure 4.2**).

4.3.4 Sensitivity Analysis

In a sensitivity analysis using when hearing was measured as baseline Year 5), the estimated effects were overall similar for rates of cognitive decline as well as incident dementia and inferences were unchanged. In models adjusted for self-reported hearing aid use, results for each analysis were again similar in magnitude and inferences did not change.

4.4 DISCUSSION

In a longitudinal investigation of 2,061 older adults over 11 years of follow-up from the Health ABC Study, moderate or greater hearing loss (vs. normal or mild loss) was associated with faster rates of cognitive decline and greater risk of incident dementia independent of depressive symptom status in all analyses. The presence of clinically significant depressive symptoms alone was associated with faster rates of cognitive change and incident dementia, particularly when symptomatology was repeated at more than one year of follow-up. While each independent condition demonstrates elevated risk for cognitive impairment, individuals with hearing loss who additionally developed depressive symptoms overall presented the greatest estimated risk for both rates of cognitive decline and risk of incident dementia – highlighting potential dementia prevention opportunities. Findings suggest the presence of depressive symptoms among hearing impaired older adults may play a modifying role in the hearing-dementia relationship. Intervention on hearing loss and depressive symptoms may have the potential to improve quality of life for a significant number of older adults in our population and clinics.

While many other studies have looked at the hearing-dementia or depression-dementia link in isolation, few have considered the risk presented by the joint presence of these two independent risk factors for dementia. Our results uniquely consider both the independent estimated effects of hearing and depressive symptoms as well as the combined presence of depressive symptoms among those with hearing loss. Further, as significant variability in

length of depressive symptoms exists, our study investigated differences in risk by longevity of depressive symptom status. Findings suggest those with clinically significant hearing loss at a level which may impair communication ability are at risk for a significantly faster rate of cognitive change as well as increased risk of incident dementia, especially among those who additionally develop clinically meaningful depressive symptomatology. Additional study of potential biological interaction or a biological vs behavioral/social mechanism behind this relationship may further inform our dementia intervention efforts.

The findings presented compliment prior research completed within the National Alzheimer's Coordinating Center data set which performed a mediation analysis of hearing loss, late-life depression, and dementia[8]. While this study did not find that depression mediated the hearing-dementia relationship, results indicated treated hearing loss (defined as participants who wore hearing aids resulting in perceived functionally normal hearing) was associated both with depression and conversion to dementia. In contrast, our analysis quantified how the combined presence of clinically meaningful depressive symptoms among those with significant hearing loss presents differing risk for cognitive change or dementia than the presence of each condition in isolation, highlighting a potential interrelated link between hearing loss, depression, and dementia which has notable clinical relevance.

A strength of our study was the investigation of the estimated effect among hearing impaired adults with the additional presence of depressive symptomatology using a variety of means to measure depression. Across ways

to measure depressive symptoms, the estimated effect on rates of cognitive decline was more consistent with DSST measures than with 3MS measures. However, our test scores were not standardized, therefore we exercise caution in comparison of rates of change across cognitive tests. It is possible the observed estimated combined effect failed to reach significance in our analysis due to our overall small sample size (i.e., 17 participants with both persistent depressive symptoms and hearing loss, 43 with baseline depressive symptoms and hearing loss). These small sample sizes may have limited power and the width of confidence intervals obtained, therefore placing constraints on available inferences.

Although our small sample size limits the inferences possible from our analysis of the combined estimated effects of hearing and depressive symptoms on cognition, the greater estimated observed effect among those with both conditions presents public health and clinical opportunity. As the ability to hear and communicate effectively has a significant influence on life and behaviors, it is possible the additional development of depressive symptomatology – particularly that lasting longer than an acute event – among those with hearing loss exacerbates psychosocial or neuropsychological buffers and may lead to accelerated cognitive decline. With this in mind, consideration of low-risk strategies which could minimize the adverse effects of each condition, such as the use of hearing aids to manage hearing loss and cognitive behavioral therapy for depressive symptoms, could have downstream beneficial impacts for older adults. Further, it is possible those with significant hearing loss who then develop

depression may be less likely to seek or adhere to clinical or public health recommendations[28-30]. However, the use of hearing aids or other forms of management for hearing loss has the potential to alter this risk landscape. In our analytic sample, we observed those with repeated depressive symptoms who developed incident dementia had nearly 10% lower prevalence (27% vs 16%) of self-reported hearing aid use compared to those who remained free of dementia at the end of follow-up. When restricting to those with a moderate or greater hearing loss only, those with depressive symptoms who reported hearing aid use showed a suggestion of, but not statistically significant, qualitatively protective effect of incident dementia and cognitive decline, although small sample size limited inference.

Our study was limited in the ascertainment of the presentation of depressive symptoms via one evaluative scale, the CES-D 10. While the CES-D is not a comprehensive medical evaluation and is subject to episodic depression or may miss certain aspects of late-life depression in older adults, the CES-D has widespread use and has demonstrated good reliability and validity of symptoms[18-19]. The number of repeat measures of CES-D 10 over time is a strength of our study. Additionally, hearing was not measured until Year 5 of the study. However, hearing generally changes very gradually at 1-2 dB per year in adults[31-32]. We therefore would expect minimal misclassification of hearing status for our analysis. We opted to consider Year 1 as our study baseline to capitalize on a longer follow-up period and richer data, particularly for depression treatment history. Additionally, results from our sensitivity analysis using Year 5 as

baseline, while reduced in magnitude, also suggested the greatest risk for cognitive change and incident dementia was among those with both conditions.

Our results highlight how consideration of comorbid conditions, each independent risk factors for dementia, could potentially present pivotal intervention options and have far-reaching benefits for older adults. Management and consideration of hearing loss in conjunction with other conditions may have beneficial effects beyond just communication ability. With the high prevalence of hearing loss among older adults and under-utilization of treatment strategies such as hearing aids, significant room for intervention and potential interruption of the hearing-depression-dementia relationship exists. While we completed sensitivity analyses with models adjusted for reported hearing aid use at baseline, our measure of hearing aid use was via self-report, leaving potential room for misclassification as many adults over-report on their hearing aid use[33]. Continued investigation of how the management of hearing loss may influence downstream psychosocial outcomes using a more specific and valid assessment of hearing aid use may greatly improve our understanding of how intervention on these measures may reduce dementia risk. Current clinical trials of hearing aid use among older adults are underway and may further aid in our understanding and quantification of the broad benefits of hearing management.

In a longitudinal cohort study of 2,061 older adults, the combined presence of moderate or greater hearing loss and depressive symptoms demonstrated the highest estimated effect on the rates of cognitive decline and risk of incident dementia. The independent effects of hearing loss and depressive

symptoms were each associated with greater risk for incident dementia. While our results warrant further investigation, clinical providers of older adults, particularly those with hearing loss, may consider co-existing psychosocial conditions such as depression. Identification of low-risk intervention options for dementia among subgroups of older adults at a particularly greater risk for cognitive decline or dementia could vastly improve public health strategies as well as quality of life for older adults.

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Table 4.1 Cross-sectional and Longitudinal Measures of Depressive Symptoms utilized

Measure	Definition
Baseline	CES-D 10 score ≥ 10 at Year 1(1997-1998) Reported treatment for depression
Persistent	CES-D 10 score ≥ 10 at the first two administrations of the CES-D at Year 1(1997-1998) and Year 3(1999-2000) Reported treatment for depression
Repeated	CES-D 10 score ≥ 10 at more than one administrations of the CES-D between Year 1(1997-1998) and Year 5(2001-2002) Reported treatment for depression

Notes: CES-D 10: Center for Epidemiologic Depression Scale short form; reported treatment for depression: self-reported treatment and/or antidepressant use intended for treatment of depression.

Table 4.2 Baseline Characteristic of the Analytic Sample in the Health ABC Study (N=2,061)

Characteristic	Overall	Normal or mild hearing loss or depressive symptoms N (%)	Moderate+ Hearing loss only N (%)	Depressive symptoms only N (%)	Moderate+ Hearing Loss & Depressive Symptoms N (%)	p-value
N	2061	1529	385	104	43	
Baseline age, mean (SD)	74.0 (2.8)	73.7 (2.8)	74.9 (2.9)	73.8 (2.8)	74.7 (2.8)	<0.001
PTA, mean (SD)	30.3 (13.5)	25.0 (8.6)	50.7 (9.1)	26.7 (7.7)	47.5 (8.5)	<0.001
BMI, kg/m2, mean (SD)	27.4 (4.7)	27.4 (4.8)	27.1 (4.1)	27.8 (4.4)	26.9 (4.2)	0.52
Black	776 (37.7)	630 (41.2)	95 (24.7)	39 (37.5)	12 (27.9)	<0.001
Women	1072 (52.0)	849 (55.5)	131 (34.0)	74 (71.2)	18 (41.9)	<0.001
Post-secondary education	1136 (55.1)	828 (54.2)	218 (56.6)	59 (56.7)	31 (72.1)	0.11
Memphis	1009 (49.0)	731 (47.8)	214 (55.6)	46 (44.2)	18 (41.9)	0.025
Marital status						0.11
Never Married	103 (5.0)	79 (5.2)	18 (4.7)	3 (2.9)	3 (7.0)	
Married	1201 (58.3)	882 (57.7)	242 (62.9)	51 (49.0)	26 (60.5)	
Widowed/Divorced/Separated	757 (36.7)	568 (37.1)	125 (32.5)	50 (48.1)	14 (32.6)	
Live alone	594 (28.8)	437 (28.6)	104 (27.0)	40 (38.5)	13 (30.2)	0.14
Diabetes	714 (34.6)	531 (34.7)	144 (37.4)	22 (21.2)	17 (39.5)	0.018
Smoking	1119 (54.3)	799 (52.3)	238 (61.8)	51 (49.0)	31 (72.1)	<0.001
Hypertension	1018 (49.4)	763 (49.9)	173 (44.9)	60 (57.7)	22 (51.2)	0.11
Stroke	158 (7.7)	121 (7.9)	25 (6.5)	9 (8.7)	3 (7.0)	0.79
Persistent Depressive symptoms	61 (3.0)	0 (0.0)	0 (0.0)	44 (42.3)	17 (39.5)	<0.001
Baseline CES-D 10, median (IQR)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	10.0 (10.0, 13.0)	11.0 (2.0, 12.0)	<0.001
Repeated Depressive symptoms	220 (10.5)	0 (0.0)	0 (0.0)	167 (8.1)	53 (2.6)	
DSST, mean (SD)	37.5 (14.1)	37.9 (14.1)	36.3 (13.7)	37.8 (15.7)	32.3 (14.7)	0.018
3MS, median (IQR)	93.0 (88.0, 96.0)	93.0 (88.0, 97.0)	92.0 (87.0, 96.0)	94.0 (88.0, 97.0)	93.0 (84.0, 96.0)	0.013

Note: Health ABC= Health, Aging, and Body Composition study; PTA= pure tone average; BMI= body mass index; CES-D 10= Center for Epidemiologic Study Depression Scale short form; persistent depressive symptoms= CES-D 10 score ≥10 on the first two evaluations; repeated depressive symptoms= more than one CES-D 10 score ≥10 during the first 4 years of follow-up; DSST= Digit Symbol Substitution Test; 3MS= Modified Mini-Mental State exam; IQR= interquartile range; Moderate+ hearing loss= moderate or greater hearing loss

Table 4.3 Independent and Joint effects of Hearing and Depressive Symptom Status on Difference in Baseline Cognitive Test Score and Rate of Cognitive over Decline per Year across Measures of Depressive Symptoms over 11 years of follow-up (N=2,061)

			Modified Mini-Mental State Exam		Digit Symbol Substitution Exam	
Hearing Loss	**Depressive Symptoms**	**N**	**Difference in Baseline score**	**Difference in change per Year (95% CI)**	**Difference in Baseline score**	**Difference in change per Year (95% CI)**
Normal Hearing or Mild Hearing Loss	*No Baseline Depressive Symptoms*	1,529	Reference	Reference	Reference	Reference
	Baseline Depressive Symptoms	103	0.17(-0.60, 0.94)	0.01 (-0.13, 0.15)	0.80 (-1.06, 2.66)	-0.11 (-0.31, 0.10)
Moderate+ Hearing loss	*No Baseline Depressive Symptoms*	385	**-0.86 (-1.53, -0.18)**	**-0.14 (-0.26, -0.02)**	-0.81 (-2.08, 0.47)	**-0.17 (-0.29, -0.05)**
	Baseline Depressive Symptoms	43	-0.78 (-2.35, 0.78)	-0.35 (-0.74, 0.04)	-2.44 (-5.21, 0.34)	-0.16 (-0.46, 0.15)
Interaction (p value)			0.91	0.31	0.15	0.54
Normal Hearing or Mild Hearing Loss	*No Persistent Depressive Symptoms*	1,589	Reference	Reference	Reference	Reference
	Persistent Depressive Symptoms	44	0.21 (-1.01, 1.42)	0.02 (-0.19, 0.23)	**-3.25 (-6.20, -0.30)**	0.01 (-0.33, 0.34)
Moderate+ Hearing loss	*No Persistent Depressive Symptoms*	411	**-0.82 (-1.50, -0.15)**	**-0.16 (-0.28, -0.04)**	-1.20 (-2.45, 0.06)	**-0.15 (-0.26, -0.04)**
	Persistent Depressive Symptoms	17	-1.46 (-4.44, 1.52)	-0.48 (-1.31, 0.35)	0.26 (-3.47, 3.99)	**-0.64 (-1.27, -0.01)**
Interaction (p value)			0.61	0.44	0.05	0.18
Normal Hearing or Mild Hearing Loss	*No Repeated Depressive Symptoms*	1,322	Reference	Reference	Reference	Reference
	Repeated Depressive Symptoms	311	**-1.34 (-2.30, -0.38)**	**-0.21(-0.37, -0.05)**	**-1.94 (-3.77, -0.11)**	**-0.21 (-0.40, -0.03)**
Moderate+ Hearing loss	*No Repeated Depressive Symptoms*	343	**-0.87 (-1.57, -0.16)**	**-0.18 (-0.30, -0.07)**	**-1.39 (-2.70, -0.08)**	**-0.16 (-0.28, -0.05)**
	Repeated Depressive Symptoms	85	**-1.91 (-3.74, -0.09)**	**-0.30 (-0.78, -0.19)**	-0.26 (-3.29, 2.77)	**-0.35 (-0.67, -0.03)**
Interaction (p value)			0.79	0.72	0.09	0.89

Note: Depressive symptom= CES-D 10 score ≥ 10 at baseline of visit 1; Persistent depressive symptoms= CES-D 10 score ≥ 10 during the first two measures of the CES-D (visit 1 and visit3); Repeated Depressive Symptoms= CES-D 10 score ≥ 10 on more than one evaluation of CES-D during first 4 years of follow-up (visits 1, 3, 4, 5); Moderate+= moderate or greater hearing loss

Figure 4.1 Estimated Mean Scores on Cognitive Test by Exposure and Measure of Depressive Symptom in the Health ABC Study over 11 years of follow-up (N=2,061)

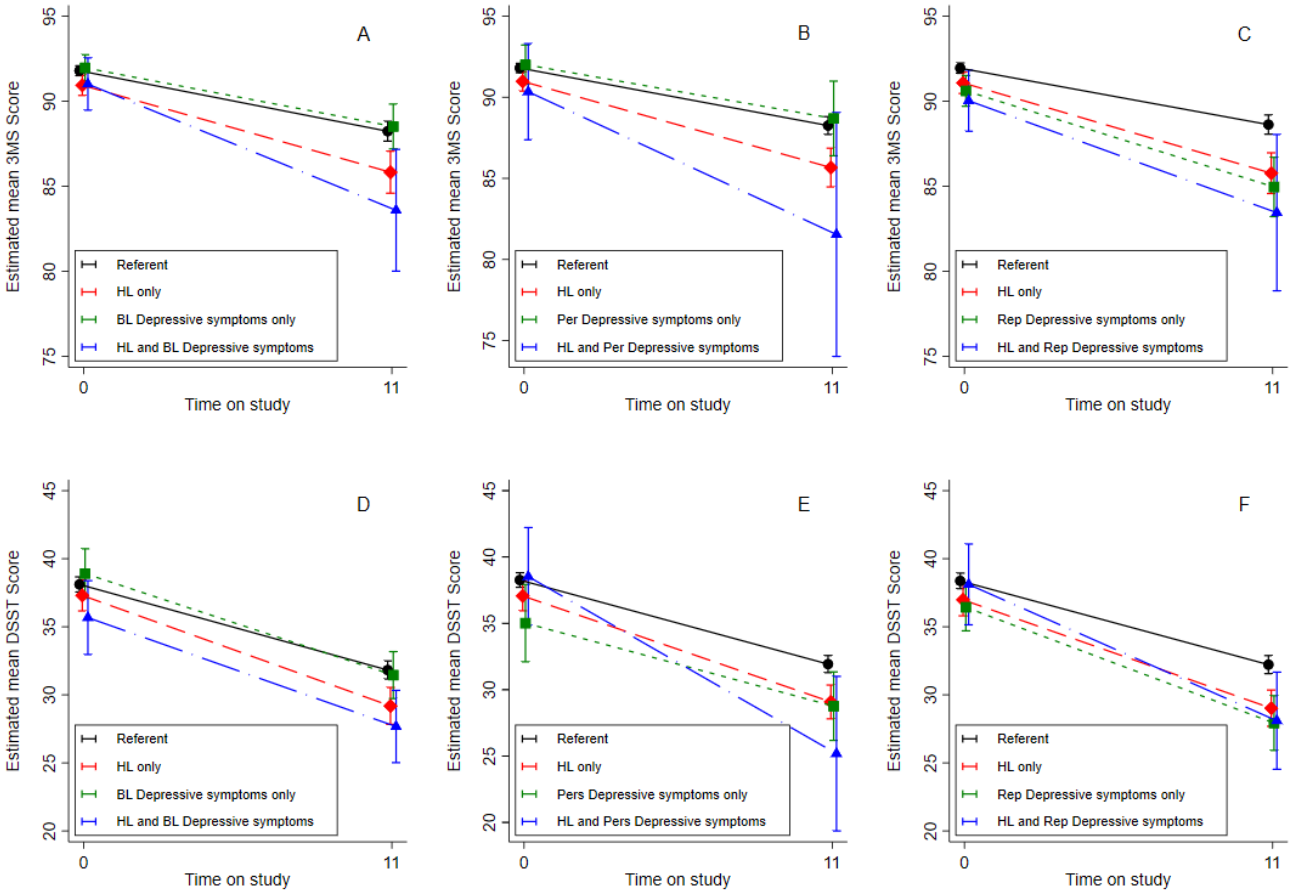

FIGURE 4.1 A. Estimated mean 3MS score over follow-up by hearing loss and baseline depressive symptoms status, B. Estimated mean 3MS score over follow-up by hearing loss and persistent depressive symptoms status, C. Estimated mean 3MS score over follow-up by hearing loss and repeated depressive symptoms status, D. Estimated mean DSST score over follow-up by hearing loss and baseline depressive symptoms status, E. Estimated mean DSST score over follow-up by hearing loss and persistent depressive symptoms status, F. Estimated mean DSST score over follow-up by hearing loss and repeated depressive symptoms status.
Notes: BL Depressive symptoms= CES-D 10 score ≥ 10 at baseline of visit 1; Pers Depressive symptoms= repeated depressive symptoms, CES-D 10 ≥ 10 at visit 1 & visit 3; Rep Depressive Symptoms= repeated depressive symptoms, CES-D 10 ≥ 10 at more than one visit between visits 1-5; HL= moderate or greater hearing loss; Referent= normal or mild hearing loss and no depressive symptoms (CES-D 10 score <10); 3MS= Modified Mini-Mental State Exam; DSST= Digit Symbol Substitution Test

Table 4.4 Multivariable-adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Joint Association between Hearing Impairment and Incident Dementia by Depressive Symptom status, Health ABC Study, N=1,820

	No Depressive Symptoms		Depressive Symptoms	
Level of Hearing Loss	N with/without Dementia	HR (95% CI)	N with/without Dementia	HR (95% CI)
Normal or Mild	145/1,233	1.00 [Ref]	11/57	1.70 (0.92, 3.15)
≥ *Moderate*	58/293	**1.42 (1.03, 1.95)**	9/14	**3.81 (1.90, 7.62)**
	No Depressive Symptoms		**Repeated Depressive Symptoms**	
Level of Hearing Loss	N with/without Dementia	HR (95% CI)	N with/without Dementia	HR (95% CI)
Normal or Mild	127/1,184	1.00 [Ref]	29/106	**2.35 (1.56, 3.53)**
≥ *Moderate*	55/275	**1.54 (1.10, 2.15)**	13/32	**2.91 (1.59, 5.33)**

RERI (95% CI) = 1.69; 95% CI (-1.10, 4.47) depressive symptoms; 0.02; 95% CI (-1.93, 1.97) repeated depressive symptoms
Synergy Index (95% CI) = 2.51; 95% CI (-0.87, 5.88) depressive symptoms; 1.01; 95% CI (-0.03, 2.04) repeated depressive symptoms
* Adjusted for age, gender, race, education, study center, marital status, living alone, BMI, hypertension, stroke history, and diabetes
Note: HR= hazard ratio; Depressive symptoms= CES-D 10 score ≥ 10 at baseline of visit 1; Repeated Depressive Symptoms= CES-D 10 score ≥ 10 on more than one evaluation of CES-D during first 4 years of follow-up (visits 1, 3, 4, 5)

Figure 4.2 Stratified hazard ratio of incident dementia for heterogeneity of effect between hearing loss and measure of depressive symptom

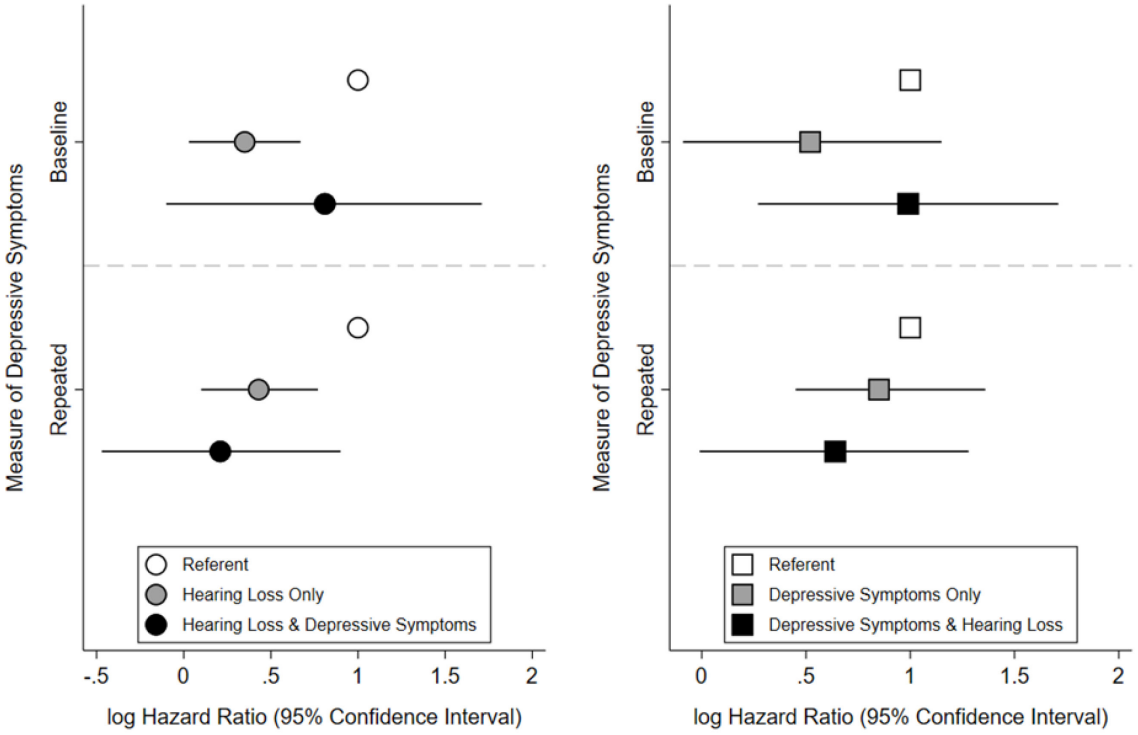

FIGURE 4.2 Left panel: hazard ratio of incident dementia among strata of hearing loss; Right panel: hazard of incident dementia among strata of depressive symptoms.
Note: Depressive symptoms= CES-D 10 score ≥ 10 at baseline of visit 1; Repeated Depressive Symptoms= CES-D; Hearing loss= moderate or greater hearing loss

CHAPTER 5: Conclusion

5.1 Summary of findings

The overall goal of this thesis was to continue our elucidation of how hearing loss may fit into a broader framework for dementia and late-life mental health. This meant first understanding what we currently know regarding the association between hearing loss and dementia, and identifying areas for research that, in our view, allow for the most substantial clinical and public health advances. In doing so, we aimed to build an understanding of how hearing loss may influence additional risk factors for dementia and how/if the combination of hearing loss with these other risk factors further influences dementia risk.

5.1.2 Chapter 2: Hearing and Cognition

While there are decades of research revolving around the contribution of age-related hearing loss to dementia risk, growing evidence of the adverse consequences of hearing loss for older adults has brought conversations about hearing health and care into the clinical exam room and to the attention of older adults and policy makers. The human and economic expense of caring for the coming wave of adults reaching or past retirement age demands interdisciplinary collaboration. Auditory science and hearing researchers have the opportunity to contribute to efforts to reduce this impact. Identification of mechanism(s) driving the association between hearing and dementia, directed hearing-dementia research for the greatest public health impact and societal needs, and thoughtful translation of this research for clinicians and patients can have a monumental impact on prevention and intervention strategies for older adults. The

interdependent and synergistic processes of hearing and cognition require careful approach. Optimizing our strategies to treat hearing loss could diminish the risk of adverse outcomes and enhance health and quality of life for older adults

5.1.3 Chapter 3: Hearing loss and Risk of Depressive Symptoms in Older Adults in the Health ABC Study

In a demographically diverse population-based cohort of 2,089 older adults in the United States with up to 10 years of follow-up, we investigated the impact of hearing loss on depressive symptoms using a comprehensive definition of depression which incorporates self-reported history of depression, medication use, and questionnaires. Those with hearing loss demonstrated significantly greater odds of clinically significant depressive symptoms at baseline and suggested greater risk for incident clinically significant depressive symptoms over follow-up. Results were robust even after covariate adjustment and consideration of a history of treatment for depression. Analysis of depressive symptoms over time suggest greater risk for a poorer depressive symptom trajectory for those with hearing loss, particularly moderate or greater loss, compared to those with normal hearing.

5.1.4. Chapter 4: Examining the Combined Estimated Effects of Hearing Impairment and Depression on Risk of Cognitive Decline and Incident Dementia in the Health ABC study

In a longitudinal cohort study of 2,061 older adults, the combined presence of moderate or greater hearing loss and depressive symptoms demonstrated a greater association with risk of incident dementia than would be expected from the independent contributions of each risk factor. The rate of cognitive decline on the Digit Symbol Substitution test was steeper among those with both moderate or greater hearing loss and repeated or persistent depressive symptoms. While the rate of change was not significant for the Modified Mini-Mental State Exam, the fastest rate of change was observed for those with both risk factors. While our results warrant further investigation, clinical providers of older adults, particularly those with hearing loss, may take into consideration co-existing psychosocial conditions such as depression when considering dementia prevention and intervention strategies. Identification of low-risk intervention options for dementia among subgroups of older adults at a particularly greater risk for cognitive decline or dementia could vastly improve public health strategies as well as quality of life for older adults.

5.2 Challenges

In analyses presented here, we acknowledge the limitations with audiologic measures completed 4 years after baseline in the Health ABC Study. We elected to use the full 10 years of rich depression measures available by

using Year 1 as baseline for our analysis. While this presents a chronological gap from when hearing was measured, for the majority of older adults, hearing changes very gradually, at a rate of 1-2 dB per year[1] and is an approach which has been used in other studies[2-3]. Thus, the time between baseline and when audiometry was performed likely only presents a minimal change in hearing for most participants. We therefore do not expect significant misclassification by hearing category – any misclassification would likely lead to a conservative estimate of the association observed between hearing and depressive symptoms across our analyses performed.

We were additionally not able to assess medication use for depression beyond year 6 in the Health ABC study. Albeit the CES-D 10 demonstrates good sensitivity in identifying those with significant depressive symptoms, it is not a diagnostic measure for depression. This assessment may incorrectly capture constructs of depression that are more appropriate for older adults and result in misclassification of depressive symptoms. It is also possible that participants were biased in their reporting of their depressive symptoms, potentially due to perceived stigma associated with depression. Additionally, our investigation of risk factor exposure and rates of cognitive change or incident dementia was limited to one/two tests of cognitive function. A more comprehensive test battery including neurocognitive assessment across multiple domains, especially memory and executive function, and using both auditory and visual modalities will further enlighten our understanding of how hearing loss in conjunction with other risk factors influences dementia risk.

While we performed sensitivity analysis adjusting for hearing aid use, our measure of hearing aid use is crude and self-reported, leaving potential room for misclassification as many adults over-report their hearing aid use[4]. Continued investigation of how the management of hearing loss may influence downstream psychosocial outcomes using a more specific and valid assessment of hearing aid use may greatly improve our understanding of how intervention on these measures may reduce dementia risk and have far-reaching public health impact. Current clinical trials of hearing aid use among older adults are underway and may further aid in our understanding and quantification of the broad benefits of hearing management.

Presenting opportunity for further research, our analyses were not able to investigate associations by central hearing ability, as measures of central hearing were not available from the Health ABC study. Further research on this association may shed light on how an individual's functional hearing ability may present differing associations than measures of peripheral hearing loss. Consideration of how central hearing ability, which has been suggested as an early marker of incident dementia, might influence vulnerability to late-life depression or the combination of neuropsychiatric conditions requires further study.

5.3 Strengths

Our review of the hearing-dementia association provided not only a comprehensive discussion of the current evidence and proposed mechanism, but

it additionally incorporated proposed targeted areas for future research which may present the largest potential public health impact. The analyses presented capitalize on the use of a well-defined and carefully designed longitudinal cohort of community-dwelling older adults. Within this cohort, we were able to complete longitudinal investigations on the association between hearing loss and depressive symptoms. By evaluating depressive symptoms over time, we quantified both how hearing loss contributed to the presence of depressive symptoms and recurrent or prolonged depressive symptomatology, which is associated with significant negative health outcomes in older adults[5-6]. We were additionally able to investigate how the variable presentation of depressive symptoms may add to the risk associated with hearing loss or influences risk of cognitive change or incident dementia.

5.4 Implications and future directions

The thesis work presented here expands on our current understanding of the influence of hearing loss on late-life mental health and depression but leaves many avenues of research open for investigation and highlights key directions for future study. In Chapter 2 we provided a detailed discussion of selected future directions for research which in our view might best inform our investigation of the potential casual association between hearing and dementia. First, we discussed elucidation of the driving mechanism behind the hearing-cognition association. If we can determine the link(s) or driver(s) behind the association of hearing loss with cognition, we may better plan for and provide appropriate

intervention options to delay the onset or alter the trajectory of the clinical course of dementia. How best to intervene, and ultimately whether treatment for hearing loss will be effective in decreasing or delaying dementia risk, largely depends on the underlying mechanism. In all likelihood, multiple mechanisms are involved in the hearing-dementia association; thus, further investigation should determine if one mechanism serves as a primary driver and how each may interact to alter risk. It is possible the primary driver is unique to the individual, allowing for a person-centered approach to intervention that alters the progression to dementia.

Next, we expressed a need to understand how treating hearing loss influences dementia risk- either directly or by also reducing the risk for other risk factors for dementia. Evidence for the impact treating hearing impairment has on cognitive decline or dementia is accumulating. However, until the results of the current longer-term clinical trials are available, the evidence of these effects on cognitive decline and dementia risk largely stem from observational studies which, while powerful in their right, present challenges for causal inference. We review how a framework of public health prevention strategies recognize the potential for targeted intervention at each stage of the disease process— known as primary, secondary, and tertiary prevention[7], and provide examples of intervention strategies at each stage of prevention. Evidence for hearing intervention at these levels of prevention remains limited, and an understanding of how hearing loss treatment throughout the process might influence upstream higher-level cognitive processing and mental health is virtually non-existent.

Lastly, in Chapter 2 we discussed a need to determine the most appropriate way to measure hearing ability among adults when estimating dementia risk. Consideration of self-reported hearing, peripheral hearing ability, central hearing ability, and electrophysiologic measures may all have a role in identifying those who may present an increased risk for dementia. Yet current research remains limited in our ability to understand how measures of different aspects of the hearing system may inform risk. Additionally, we must also ensure we maintain fidelity of cognitive tests among those with hearing impairment, or any sensory impairment, as well as of sensory evaluation among those with more advanced cognitive impairment.

The analyses presented in this thesis presented additional future directions for research. There is need for detailed investigation of social influences by race and gender or other identifying factors on the association between hearing loss and late-life mental health. While evidence for associations between hearing loss and late-life mental health has been growing, what has received minimal attention is how social constructs, stressors, and demands related to personal characteristics like race and gender may influence the associations observed. Known differences in the prevalence of late-life mental health conditions, including late-life depression and dementia, by race and/or gender exist[8-9]. Late-life depression is more prevalent in women compared to men, yet these differences are shown to decrease after age 85[10-11]. Women traditionally rely on communication to maintain intimacy and connectedness and to find social support among friends[12]. Investigation of if hearing loss impedes

this connection which has been linked to decreased depressive symptoms may foster identification of avenues for prevention or intervention for novel means of supporting connection. Understanding how social factors across cohorts of older adults may influence this social support and social networks may further highlight ways in which we may support older women or men with hearing loss, both in prevention of depression, but also as a means of intervention for dementia or other mental health outcomes.

Further, minority adults have been shown to generally present with higher levels of depressive symptomatology but lower levels of major depressive disorder compared to non-Hispanic white adults in the U.S.[10,13]. Decades of social stressors, disparities, and reduced uptake of health services are hypothesized to increase vulnerability of minority adults in the U.S. to depressive symptomatology[8]. How the additional presence of hearing loss may add to these stressors or prolong poorer depressive symptom trajectory requires more detailed study. Additionally, how the mental-health stressors experienced by minority older adults with hearing impairment in the U.S. may further increase dementia risk requires more investigation but may again spotlight potential avenues for prevention or intervention.

5.5 Implications for clinical practice

How auditory scientists, cognitive scientists, epidemiologists, and other investigators present the research on hearing and cognitive impairment can have significant implications for how clinical providers educate patients and their

families, as was discussed extensively in Chapter 2. We posited how, given the varied disciplines involved in research on hearing and cognitive impairment, understanding how to synthesize the current evidence, translate findings, and guide future research for scientific progression is vital. However, current research has primarily remained siloed within disciplines. Auditory science and cognitive science researchers have the opportunity and expertise to address aspects of the primary research gaps described above. Transparency of and careful consideration of study design, measurement tools implemented, and discussion of results' applicability for clinical or community populations is essential to characterize the role of hearing impairment within the dementia timeline and meet the needs of our current and future older adults.

The growing prevalence of older adults means parallel growth in the number of hearing impaired older adults. This growth necessitates early intervention and exploration of preventive measures amenable to the unique and often complex needs of this population. The interdependence of hearing loss and neuropsychiatric disorders may provide opportunity for interdisciplinary intervention and concomitant benefit on outcomes beyond the proposed target of depression or dementia. Prior work has demonstrated feasibility and potential benefit of the use of hearing aids as a therapeutic agent for depression. Exploration of paths between individual behaviors and successful hearing aid use may improve therapeutic effectiveness by providing a non-pharmacological, low risk and under-utilized approach for late-life depression or dementia and may supplement current management strategies. Reducing the clinical and social

burden of these conditions through aural rehabilitation and combined intervention strategies could have far-reaching incidental benefit. Appropriately identifying patient candidates who could most benefit from targeted social or aural rehabilitation intervention improves the effectiveness of valuable patient-provider interactions and maximizes the potential for success. Investigation on how accounting for hearing loss may improve patient's understanding of medical recommendations, treatment compliance, or effectiveness when paired with non-pharmacological treatments is in its infancy. However, this mindfulness towards care may shed light on how considerations of hearing loss and its negative down-stream consequences may have broad implications for health services and related outcomes.

With additional insight gained, we may further be able to determine during patient interactions when may be most advantageous to intervene on hearing loss. It is possible initiation of hearing aid use for neuropsychiatric conditions may be less effective than simple employment of communication strategies to address hearing loss, or that initiation should be delayed/initiated during specific times within the mental-health management process. It is also possible initiation of hearing aid use once certain symptomatology has manifested is ineffective due to already altered brain pathology. This suggests early adoption of hearing aids upon identification of hearing loss prior to the onset of late-life mental health concerns may be a more effective management strategy and may support arguments for hearing screenings for older adults.

Our results additionally highlight the inter-relational connection between medical conditions for older adults. These findings underscore how a multi-domain approach for intervention and prevention of late-life mental health concerns may provide a more comprehensive person-centered approach to care. Our results support prior work demonstrating an association between hearing loss and depressive symptoms as well as dementia. Moreover, our results suggest greater risk of poorer cognitive outcomes among those with both hearing loss and significant depressive symptoms – greater than that expected by the presence of both conditions in isolation. While attentiveness to multimorbidity in dementia prevention has been considered in past trails such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) Study[14], inclusion of hearing within this approach to intervention design has been limited. However, consideration of hearing loss within a multimodal intervention for in-patient delirium has shown promise[15]. Hearing loss has been associated in epidemiologic work with many negative health outcomes for older adults[16-18], many of which may also increase risk for dementia or other late-life mental health conditions[19]. Thus, primary care or geriatric providers may consider hearing loss or the management of hearing loss within the context of multimorbidity, potentially as a means of both intervention and prevention for late-life mental health conditions.

5.6 Conclusion

Our working knowledge of the association between hearing loss and cognition has drastically expanded over recent decades. However, gaps in understanding and avenues for targeted research remain and leave significant room for public health intervention given the high prevalence of hearing loss among older adults. We found evidence supporting an association between hearing loss and negative late-life mental health outcomes. Specifically, we conclude hearing loss may increase risk of depressive symptoms in older adults. Furthermore, the presence of both hearing loss and depressive symptoms, each independent risk factors for dementia, resulted in steeper rates of cognitive decline and highest estimated risk for dementia. Consideration of hearing loss and its management strategies within health care and research settings may open doors for innovative intervention strategies and reduced late-life mental health conditions, improving both public health and quality of life for older adults.

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LIST OF APPENDICES

Appendix A.1 Model fit statistics for determination of class number for Depressive Symptom Trajectory

	1 class	2 class	3 class	4 class
AIC	42285.21	41934.55	41576.24	41492.46
BIC	42336.01	42002.28	41672.19	41610.99
LMR LRT p	N/A	0.000	N/A	N/A
Boot LRT p	N/A	0.000	0.00	0.00
Entropy	N/A	0.852	0.742	0.7
Latent Class 1 (%)	2089 (100%)	1877 (89.85%)	566 (27.1%)	377 (18.0%)
Latent Class 2		237 (11.33%)	1390 (66.6%)	86 (4.1%)
Latent Class 3			132 (6.3%)	601 (28.8%)
Latent class 4				1025 (49.1%)

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Education

Johns Hopkins University
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PhD candidate, Bloomberg School of Public Health, Epidemiology — August 2017-Present
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University of North Carolina
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Fellowships and Grants

- Cochlear Center on Hearing Loss and Public Health Fellow (2018-present)
  - Access to a multi-disciplinary team of experts who specialize in studying the impact of hearing loss on older adults and public health. Receives training on designing and implementing research studies as well as intervention strategies to improve health; attends seminars, hosts journal clubs and presents at research conferences
- T32 Epidemiology and Biostatistics of Aging Training Program (2017-2019)
  - Interdisciplinary training and collaboration regarding the conduct and methodology of public health research in older adults
- Pediatric Audiology Training Grant (2009-2011)
  - Completed over 400 hours of pediatric clinical training at various clinical sites.
  - Presented a poster at the UNC Student Research Forum on the feasibility of using various school hearing screening methods in Guatemala.
- Leadership Education in Neurodevelopmental Disabilities (LEND) Training Grant (2009-2011)
  - Completed a year-long course with 4 other health related disciplines that focuses on how to effectively collaborate with interdisciplinary groups in order to serve individuals with disabilities.

Certifications

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  - The association between hearing loss and diabetes
  - Speech-in-noise performance and depressive symptoms in older adults
  - Self-Report Hearing and Falls in NHIS
  - Systematic Review of Sensory Bias in Neurocognitive Research
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- **Invited Panelist. *Audiology with an Emphasis on public health applications.* American Speech-Language Hearing Association Special Interest Group: Audiology and Public Health; February 25, 2021.**
- **Powell DS, Betz J, Yaffe K, Kritchevsky S, Strotmeyer E, Simonsick E, Lin F, Gross A, Deal J. Hearing Impairment and Risk of Depression in Older Adults in Health ABC. Gerontological Society of America Conference; November 2020 (*oral presentation*)**
- **Powell DS, Kuo P, Deal JA, Gross AL. The Relationship of APOE ε4 to the Relative Times and Hazards of Dementia. Cognitive Aging Conference, Atlanta, GA, April 16, 2020. (*poster presentation accepted-conference postponed)***
- **Reed NS, Garcia EE, Powell DS, Lin FR, Palta P, Deal JA. Impaired Speech in Noise and Depressive Symptoms in Older Adults. 2020 Scientific Technology Meeting of the American Auditory Society, Scottsdale, AZ, March 5-7, 2020. (*poster presentation,* Powell DS presented)**
- **Powell DS, Kuo P, Deal JA, Gross AL. The Relationship of APOE ε4 to the Relative Times and Hazards of Dementia. Gerontological Society of America Conference; November 13-17, 2019. Austin Tx. (*oral presentation)***
- **Powell DS, Deal J, Sharrett A, Lin F, Gross A. Hearing Loss and Mental Health Outcomes in Older Adults: A Proposal. Cochlear Center Research Day. Baltimore, Maryland. March 25, 2019. (*poster presentation)***
- **Powell DS, Deal J, Gross A. Hearing Loss and Mental Health Outcomes in Older Adults. Epidemiology and Biostatistics of Aging Research in Progress. Baltimore, Maryland. February 11, 2019. (*oral presentation)***
- **Powell DS, Neiman C. Innovations in Hearing Care. Broadmead Retirement Center. Baltimore, Maryland. October 15, 2018 (*community oral presentation*)**
- **Powell DS, Mamo S, Sundberg J, Roush J. Cultural Competency: Lessons from Community-Based Learning in Guatemala. North Carolina American Academy of Audiology, 2010 (*poster presentation)***

Publications

- **Powell DS,** Deal JA, Goman AM. Reconsidering Those with Normal Hearing. *JAMA Otolaryngology*. 2020; 146(1), 67-68.

- **Powell DS, Garcia Morales E, Pletnikova S, Deal J, Reed N. Self-Report Hearing and Injury or Falls in Older Adults from the National Health and Information Survey. [*Seminars in Hearing,* In press]**
- **Powell DS, Kuo P, Qureshi R, Coburn S, Knopman D, Palta P, Gottesman R, Griswold M, Albert M, Deal J, Gross A. The Relationship of APOE ε4, Race, and Sex on the Age of Onset and Risk of Dementia.[Under Review at *Neurology*]**
- **Powell DS, Oh E, Lin FR, Deal JA. Hearing and Cognition in an Aging World. [*Journal of the Association of Research on Otolaryngology,* In press]**
- **Powell DS, Oh E, Reed N, Lin FR, Deal JA. Hearing and Cognition in an Aging World. [Invited and accepted abstract for special issue of *Frontiers in Aging-Neuroscience].***

Technical Reports and other Manuscripts

- **Powell DS, Deal JA. Hearing and Dementia- A Look Ahead. Minnesota Academy of Audiology Annual Newsletter; January 2021.**
- **Contributing author of background paper.** World Report on Hearing. Geneva: World Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO

Professional Development

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- Society of Epidemiologic Research
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    - Sensory Loss Interest Group
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Trainings and Certificates

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- *JAMA Otolaryngology*
- *Ear and Hearing*
- *Otolaryngology- Head & Neck Surgery*

- *Nature-Scientific Reports*
- *Speech Language Hearing*

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    - *Principles of Epidemiology* (2018)
    - *Epidemiologic Methods II (2018)*
    - *Introduction to Hearing Aids Course (Spring 2012)*

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        - *1 lecture and Measurement Lab on hearing measures*
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- Graduate Research Assistant: Cochlear Center for Hearing and Public Health (summer 2018-present)
- Johns Hopkins Epidemiology Doctoral Student Representative
- Johns Hopkins Epidemiology Centennial Celebration Student leader
- Johns Hopkins Bloomberg School of Public Health Research on Aging Showcase Co-President
- Johns Hopkins Cochlear Center for Hearing and Public Health Journal Club Coordinator
- Ruth Uppercru Paul Fund
    - Member of Committee through the GW Medical Faculty Associates in establishing a need-based fund and program to provide hearing aids and services to Greater Washington DC area residents; creating a sustainable and community oriented program and research.
- Coalition for Global Hearing Health- Advocacy Committee (October 2015-2017)